



Decree of the Ministry of Industry and Trade of  
the Russian Federation dated 14.06.2013 No. 916  
(as amended on 18.12.2015)  
"On approval of the Good Manufacturing Practice"  
(registered by the Ministry of Justice of the  
Russian Federation on 10.09.2013; Registration  
No. 29938)

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The Good Manufacturing Practices of the EAEU were adopted by the Decision of the Council of the Eurasian Economic Commission on 03.11.2016 under No. 77. See Article 20. of the Agreement of Common Principles and Rules of Circulation of Medicinal Products within the Eurasian Economic Union for application.

### Document name

Decree of the Ministry of Industry and Trade of the Russian Federation dated 14.06.2013, Registration No. 916

(as amended on 18.12.2015)

"On approval of the Good Manufacturing Practice"

(Registered by the Ministry of Justice on 10.09.2013, Registration No. 29938)

Registered by the Ministry of Justice of the Russian Federation on September 10, 2013. No. 29938

**MINISTRY OF INDUSTRY AND TRADE OF THE RUSSIAN FEDERATION**

**DECREE**  
**dated June 14, 2013 No. 916**

**"ON APPROVAL OF GOOD  
PRACTICE GUIDELINES**

List of amending documents  
(as amended by the Decree of the Ministry of Industry and Trade of the Russian Federation on 18.12.2015, Registration No. 4148)

In accordance with paragraph 1 of Article 45 of the Federal Law No. 61-FZ dated April 12, 2010, "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Article 1815; 2012, No. 26, Article 3446; 2014, No. 43, Article 5797; No. 52, Article 7540; 2015, No. 10, Article 1404; No. 27, Article 3951; No. 29, Article 4359, Article 4367; official online platform for legal information <http://www.pravo.gov.ru>, 15.12.2015, No. 0001201512150001) and sub-paragraph 5.2.18(31-1) of the Russian Federation Government resolution No. 1283 dated 28.11.2015 "On the Ministry of Trade and Industry" (Collected Acts of the Russian Federation, 2008, No. 24, Article 2868; 2009, No. 3, Article 378; No. 25, Article 3065; 2010, No. 6, Article 649; No.9, Article 960; 2011, No. 43, Article 6079; No. 46, Article 6523; No. 47, Article 6662; 2012, No. 43, Article 5886; 2013, No. 23, Article 2909; 2014, No. 9, Article 923; No. 37, Article 4961; 2015, No. 14, Article 2118; No. 27, Article 4080; No. 40, Article 5563; No. 44, Article 6136; No. 49, Article 6976), it is ordered as follows:  
(premise as amended by the Decree of the Ministry of Industry and Trade of the Russian Federation No. 4148 dated 18.12.2015)

1. to approve the attached [Principles](#) of the Good Manufacturing Practice.  
(as amended by the Decree of the Ministry of Industry and Trade of the Russian Federation on 18.12.2015, Registration No. 4148)

2. The execution of decree shall be supervised by

Minister  
D.V. MANTUROV

Approved by  
the Decree of the Ministry of Industry and Trade of the Russian Federation  
dated June 14, 2013 No. 916

**GOOD MANUFACTURING  
PRACTICE GUIDELINES**

List of amending documents  
(as amended by the Decree of the Ministry of Industry and Trade of the Russian Federation on 18.12.2015, Registration No. 4148)

**I. GENERAL**

1. The Good Manufacturing Practice Guidelines (GMP) provide guidance applicable to operations in

manufacture and quality control of medicines for human and veterinary use.  
(as amended by the Decree of the Ministry of Industry and Trade of the Russian Federation on 18.12.2015,  
Registration No. 4148)

2. The principles of GMP are applicable to all medicines and operations in manufacture and quality control and set specific requirements to manufacture of certain types of medicines.

3. The GMP Guide as a whole does not cover safety aspects for the personnel engaged in manufacture, nor aspects of protection of the environment, safety aspects in case of fire or explosion, chemical and sanitary and hygienic safety aspects, as well as other types of safety aspects occurring during the manufacture of medicines. In such cases, appropriate measures should be taken in accordance with the normative regulations of the Russian Federation.

## II. TERMS AND DEFINITIONS

4. The following terms and definitions are used herein:

cylinder - container usually cylindrical suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature;

biological agents - microorganisms, including genetically engineered microorganisms, cell cultures and endoparasites, whether pathogenic or not;

biogenerator- contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to effect their multiplication or their production of other substances by reaction with the other materials. Biogenerators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal;

validation - a documented program that provides a high degree of assurance that a specific process, method, equipment, material, operation or system meet given requirements and their use will consistently produce a result meeting pre-determined acceptance criteria;

return - sending a medicinal product back to its manufacturer or distributor;

air lock - an enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or materials;

highly active materials - chemical compounds that affect human body at low concentrations;

highly active medicines - medicines that have pharmacological effect at low concentrations;

finished product - a medicinal product which has undergone all stages of production, including packaging in its final container;

record - a document used to manage and record GMP compliance;

contained area - area equipped with appropriate air handling and filtration as to prevent contamination of the external environment with biological agents from within this area;

containment - the action of confining a biological agent or other entity within a defined space;

secondary containment - a system of containment which prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of airlocks and/or sterilisers for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

primary containment - a system of containment which prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with

secure operating procedures;

infected - contaminated with extraneous biological agents and therefore capable of spreading infection;

starting material - a material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance;

calibration - the set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard;

quarantine- the status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal;

qualification- action of proving that any equipment or auxiliary systems are installed and work correctly and actually lead to the expected results. The word validation is sometimes widened to incorporate the concept of qualification;

cell culture - the result from the in-vitro growth of cells isolated from multicellular organisms;

manifold- equipment or apparatus designed to enable one or more gas containers to be cleaned and filled simultaneously from the same source;

computerised system- a system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control;

controlled area- an area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination, and the consequences of accidental release of living organisms. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants. The level of control exercised should reflect the nature of the organism employed in the process;

in-process control- checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms its specification. The control of the environment or equipment may also be regarded as a part of in-process control;

quality control- quality control is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures;

cryogenic vessel- a container designed to contain liquefied gas at extremely low temperature;

medicinal plant- a plant the whole or part of which is used for medicinal purpose;

medicinal product- any substance or combination thereof coming in contact with the human or animal body, penetrating into the organs and tissues of the human or animal body, used for prophylaxis, diagnostics (except for substances or combinations thereof not coming in contact with the human or animal body), treatment of disease, rehabilitation, as well as for maintenance, prevention or interruption of pregnancy, as may be derived from blood, blood plasma, human or animal organs and tissues, plants and minerals by synthesis methods or using biological technologies. Medicines include pharmaceutical substances and medicinal products;

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Paragraph 1, Article 4, Federal Law No. 61-FZ of 12.04.2010 "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Art. No.1815)

herbal medicinal product- a medicinal product manufactured or compounded of one type of herbal medicinal raw material or several types of such raw materials and being distributed as packed in the secondary (retail) packaging;

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Paragraph 14, Article 4, Federal Law No. 61-FZ of 12.04.2010 "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Art. No.1815)

reconciliation- a comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used;

bulk product- any product which has completed all processing stages up to, but not including, final packaging;

batch number (lot number)- a unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. The batch number uses Arabic numerals, the last four digits whereof give the month and the year of production;

cross-contamination- contamination of a starting material, of a material or of a product with another starting material, material or product;

reprocessing- reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production- Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e. g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing;

recovery- the introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture;

cell culture:

cell bank system- a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank (passages). During routine production the master cell bank is used to prepare a working cell bank. For safety and efficiency reasons, the cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production. This history and number of passages should be recorded for all master and working cell banks;

master cell bank- a culture of cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. Master cell bank is usually stored at -70 °C or lower, or is kept lyophilised at a given temperature that assures stability;

working cell bank - a culture of cells derived from the master cell bank and intended for use in the preparation of production; A working cell bank is distributed uniformly into a number of containers which are stored in the same way as master cell banks;

production- intermediate, bulk and finished products;

manufacturer- manufacturer of medicinal products - an institution manufacturing medicines in accordance with the Federal Law No. 61-FZ dated April 12, 2010, "On Circulation of Medicines"

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Collected Acts of the Russian Federation, 2010, No. 16, Article 1815.

manufacturing- is an activity in manufacturing of medicines carried out by institutions engaged in manufacturing of medicines at one, several or all stages of the technological process, as well as in storage and distribution of produced medicinal products, including all operations and control of purchase of materials and products, production, packaging, repacking, labeling, relabeling, release, storage and distribution of produced medicinal controls;

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Paragraph 31, Article 4, Federal Law No. 61-FZ of 12.04.2010 "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Art. No.1815)

intermediate product - a partly processed material, which should undergo further preparation steps before it becomes a bulk product. In relation to active substances, intermediate is a material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated during production.

procedure - description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate product, a pharmaceutical substance or a medicinal product;

herbal medicinal raw material- a fresh or dried plants or parts thereof used for manufacturing of medicines by institutions producing medicines, or for compounding of medicinal products by pharmacy institutions, veterinary pharmacy institutions and individual entrepreneurs holding pharmaceutical license;

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Paragraph 13, Article 4, Federal Law No. 61-FZ of 12.04.2010 "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Art. No.1815)

batch (lot)- a defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous within specified limits. For the control of the finished products, a batch of a proprietary medicinal product comprises all units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of continuous production process, all the units manufactured in a given period of time. To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of production, characterized by its intended homogeneity. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval;

liquifiable gases- those which, at the normal filling temperature and pressure, remain as a liquid in the cylinder;

system - a regulated pattern of interacting activities and techniques which are united to organize production and quality control of medicinal products;

cell bank system - a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank. A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production;

specification- a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria;

sterility- absence of living organisms. The conditions of the sterility test are given in the appropriate General Pharmacopoeia, Pharmacopoeia, normative documentation or normative document;

production- all operations involved in the preparation of a medicinal product or active substance, from receipt of materials, through processing and packaging, to its completion as a finished product;

packaging - all operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product

being the filled, but not finally packaged, primary containers;

packaging material - any material employed in the packaging of a medicinal product, pharmaceutical substance or intermediate product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product;

qualified person- an employee employed by the manufacturer of medicinal products, who has higher pharmaceutical, chemical or biological education or veterinary education for the manufacturing of the medicines for veterinary use, and at least five years' experience in the area of good manufacturing practice and quality control of medicines and certified according to the procedure established by the authorized federal executive body;

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Paragraph 7, Article 45, Federal Law No. 61-FZ of 12.04.2010 "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Art. No.1815)

clean area - an area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area. Clean areas groups are defined in [Annex No. 1](#) hereto;

clean contained area- an area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time;

exotic organism - a biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the given country or geographical area.

### III. BASIC REQUIREMENTS FOR PRODUCTION AND QUALITY CONTROL OF MEDICINAL PRODUCTS (PART I)

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Hereinafter, the numbering of structural units in brackets is given in compliance with GMP EC.

#### PHARMACEUTICAL QUALITY SYSTEM (CHAPTER 1)

##### Principle

5. The manufacturer must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization or Clinical Trial Authorization, as appropriate and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management. This requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by its distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practice and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Pharmaceutical Quality System should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. The basic concepts of Quality Management, Good Manufacturing Practice and Quality Risk Management are inter-related.

##### Pharmaceutical Quality System

6. (1.1) Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use.

7. (1.2) GMP applies to the life cycle stages of medicinal products: from the manufacture of investigational medicinal products, technology transfer, commercial manufacturing through to product discontinuation. However



the Pharmaceutical Quality System can extend to the pharmaceutical development life cycle stage, which should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

8. (1.3) The size and complexity of the company's activities should be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally demonstrated at the site level.

9. (1.4) A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:

a) (i) Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

b) (ii) Product and process knowledge is managed throughout all life cycle stages;

c) (iii) Medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice;

d) (iv) Production and control operations are clearly specified and Good Manufacturing Practice adopted;

e) (v) Managerial responsibilities are clearly specified;

f) (vi) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain;

g) (vii) Processes are in place to assure the management of outsourced activities;

h) (viii) A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;

j) (ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future;

k) (x) All necessary controls on intermediate products, and any other in-process controls and validations are carried out;

l) (xi) Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;

m) (xii) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;

n) (xiii) After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality

o) (xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. This can be determined using Quality Risk Management principles. In cases where the true root cause of the issue cannot be determined, consideration should be given to identifying the most likely root cause. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system-based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventative actions should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles;

p) (xv) Medicinal products are not sold or supplied before a Qualified Person has certified that each

production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation or GMP;

r) (xvi) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

q) (xvii) There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System.

10. (1.5) Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.

11. (1.6) There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.

12. (1.7) The Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

#### Good Manufacturing Practice and Quality Control for Medicinal Products

13. (1.8) Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification.

14. The basic requirements of GMP are that:

a) (i) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;

b) (ii) Critical steps of manufacturing processes and significant changes to the process are validated;

c) (iii) All necessary facilities for GMP are provided including:

appropriately qualified and trained personnel;

adequate premises and space;

suitable equipment and services;

suitable raw and packaging materials;

approved procedures and instructions, in accordance with the Pharmaceutical Quality System;

suitable storage and transport;

d) (iv) Instructions and procedures are written in an instructional form in clear and unambiguous language;

e) (v) Procedures are carried out correctly and operators are trained to do so;

f) (vi) Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected;

g) (vii) Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;

h) (viii) Records of manufacture including distribution which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;

j) (ix) The distribution of the products minimises any risk to their quality and takes account of Good Distribution Practice;

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Decree of the Ministry of Healthcare and Social Development of the Russian Federation No. 1222n dated December 28, 2010 "Guidelines for Wholesale Trade in Medicinal Products" (registered by the Ministry of Justice of the Russian Federation, Registration Number 19698).

k) (x) A system is available to recall any batch of product, from sale or supply;

l) (xi) Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

#### Quality Control

15. (1.9) Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that:

a) (i) Adequate facilities, trained personnel and approved procedures are available for sampling and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

b) (ii) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by approved personnel and methods;

c) (iii) Test methods are validated;

d) (iv) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

e) (v) The finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;

f) (vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

g) (vii) No batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorisations in accordance with [Annex No. 16](#) thereto;

h) (viii) Sufficient reference samples of starting materials and products are retained in accordance with [Annex N18](#) to permit future examination of the product. Samples of finished products should be retained in the final pack excluding samples of large size, weight or parameters.

#### Product Quality Review

17. (1.10) Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews.

18. Quality reviews should include at least:

a) (i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances;

b) (ii) A review of critical in-process controls and finished product results;

c) (iii) A review of all batches that failed to meet established specification(s) and their investigations;

d) (iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;

e) (v) A review of all changes carried out to the processes or analytical methods;

f) (vi) A review of Marketing Authorisation variations submitted, granted or refused, including those for export only dossiers.

g) (vii) A review of the results of the stability monitoring programme and any adverse trends;

h) (viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time;

j) (ix) A review of adequacy of any other previous product process or equipment corrective actions;

k) (x) For new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments;

l) (xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc;

m) (xii) A review of any contractual arrangements as defined in [segments 237 -255](#) hereto to ensure that they are up to date.

19. (1.11) The manufacturer and, where different, marketing authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection.

20. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

21. Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the product quality review.

#### Quality Risk Management

22. (1.12) Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

23. (1.13) The principles of quality risk management are that:

a) (i) The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

b) (ii) The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

## PERSONNEL (CHAPTER 2)

### Principle

24. The correct organization and functioning of quality management system, as well as manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

### General

25. (2.1) The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

26. (2.2) The manufacturer must have an organisation chart. People in responsible positions should have specific duties recorded in written job descriptions. These individuals should have adequate authority to fulfill their responsibilities. The duties of these individuals may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

### Key personnel

27. (2.3) Key personnel include the head of production, the head of quality control, and if at least one of these persons is not responsible for batch release of the product, the responsible manager or other competent persons designated for the purpose. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organizations, it may be necessary to delegate some of the functions listed in [segments 30 - 32](#) hereto other competent persons.

28. (2.4) The duties of the responsible manager can be summarized as follows:

a) (a) a responsible manager must ensure that each batch of medicinal products produced in the Russian Federation has been produced and tested in accordance with the regulatory requirements of the Russian Federation and the marketing authorization;

b) (b) a responsible manager must ensure that each imported batch of medicinal products produced outside the Russian Federation has undergone, in the importing country, testing in accordance with the regulatory requirements of the Russian Federation;

c) (c) a responsible manager must certify in a register or document before release that each production batch satisfies the requirements.

The persons responsible for these duties must meet the qualification requirements of the Russian Federation. The authorized persons must be at the disposal of the authorization holder at all times. Their responsibilities may only be delegated to other qualified personnel.

30. (2.5) The Head of Production generally has the following responsibilities:

a) (i) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;

b) (ii) b) to approve the instructions relating to production processes and to ensure that these instructions are strictly observed;

c) (iii) to evaluate production records and to ensure that these are checked and signed by the responsible manager before they are sent to the quality control department;

d) (iv) to check the maintenance of his department, facilities and equipment;

e) (v) to ensure that the appropriate validations are done;

f) (vi) to ensure that required initial and continuing training of his department personnel is carried out;

31. (2.6) The head of quality control generally has the following responsibilities:

a) (i) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products;

b) (ii) to evaluate batch records;

c) (iii) to ensure that all necessary testing is carried out;

d) (iv) to approve specifications, sampling instructions, test methods and other quality control procedures;

e) (v) to approve and monitor any contract analysts specified in [sections 237 - 255](#) hereto (contract testing);

f) (vi) to check the maintenance of his department, facilities and equipment;

g) (vii) to ensure that the appropriate validations are done;

h) (viii) to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

32. (2.7) The heads of production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:

the implementation or amendment of written procedures and other documents along with their supplements;

the monitoring and control of the manufacturing environment;

plant hygiene;

process validation;

training;

the approval and monitoring of suppliers of materials;

the approval and monitoring of contract manufacturers specified in [sections 237 - 255](#) hereto (contractual manufacturer);

the designation and monitoring of storage conditions for materials and products;

the retention of records;

the monitoring of compliance with the requirements of Good Manufacturing Practice;

the inspection, investigation and taking of samples, in order to monitor factors which may affect product quality.

#### Training

33. (2.8) The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

34. (2.9) Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be approved by either the head of product or the head of quality control. Training records should be kept.

35. (2.10) Personnel working in areas where contamination is a hazard e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

36. (2.1) Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. Where this is unavoidable, they should be given sufficient information (particularly about personal hygiene and the protective clothing provided). They should be closely supervised.

37. (2.12) The concept of Quality Assurance and all measures to facilitate its understanding, implementation, and improvement should be fully discussed during the training sessions.

#### Personnel Hygiene

38 (2.13) Detailed hygiene programs should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programs should be encouraged by management and widely discussed during training sessions.

39. (2.14) All personnel should receive medical examination upon recruitment. It is the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

40. (2.15) Practicable steps should be taken to ensure that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of pharmaceutical products.

41. (2.16) Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

42. (2.17) Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected, should be forbidden.

43. (2.18) Direct contact should be avoided between the operator's hands and the product as well as with any part of the equipment that comes into contact with the products.

44. (2.19) Personnel should be instructed to use the hand-washing facilities.

45. (2.20) Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in [Annex No. 1](#) and [Annex No. 5](#) hereto.

### PREMISES AND EQUIPMENT (CHAPTER 3)

#### Principle

46. Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any

adverse effect on the quality of products.

## Premises

### General

47. (3.1) Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

48. (3.2) Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

49. (3.3) Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

50. (3.4) Premises should be designed and equipped so as to afford maximum protection against the entry of pest or other animals.

51. (3.5) Steps should be taken in order to prevent entry of unauthorized persons into premises. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

### Production area

52. (3.6) In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e. g. penicillins) or biological preparations (e. g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-pharmaceutical products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made.

53. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

54. (3.7) Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

55. (3.8) Adequate working and in-process storage space should be provided to permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

56. (3.9) Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

57. (3.10) Piping, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, they should be accessible from outside the manufacturing areas during maintenance.

58. (3.11) Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible. But if necessary, they should be sufficiently shallow to permit cleaning and disinfection.

59. (3.12) Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations



undertaken within them and to the external environment.

60. (3.13) Weighing of starting materials should usually be carried out in a separate room designed for weighing purpose.

61. (3.14) In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.

62. (3.15) Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

63. (3.16) Production areas should be well lit, particularly where optical on-line controls are carried out.

64. (3.17) In-process controls may be carried out within the production area provided they do not carry any risk for the production.

#### Storage Areas

65. (3.18) Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products, including: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

66. (3.19) Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e. g. temperature, humidity) these should be provided, checked and monitored.

67. (3.20) Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

68. (3.21) Where segregated storage areas are designated for quarantining, these areas must be clearly marked and their access restricted to authorized personnel. Any system used in place of the physical quarantine should give equivalent security.

69. (3.22) There should normally be a separate "sampling area" for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

70. (3.23) Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

71. (3.24) Highly active materials or products should be stored in safe and secure areas in accordance with the normative regulations of the Russian Federation.

72. (3.25) Printed packaging materials should be considered critical to the conformity of the pharmaceutical product and special attention should be paid to the safe and secure storage of these materials.

#### Quality Control Areas

73. (3.26) Normally, quality control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biological or microbiological materials and radioisotopes, which should also be separated from each other.

74. (3.27) Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

75. (3.28) Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

76. (3.29) Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples, if not otherwise specified by regulatory requirements of the Russian Federation.

#### Ancillary Areas

77. (3.30) Resting and cafeteria areas should be separate from other areas.

78. (3.31) Facilities for changing clothes, and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

79. (3.32) Maintenance workshops should as far as possible be separated from production areas. Whenever spare parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

80. (3.33) Animal houses should be well isolated from other areas, with separate entrance and separate ventilation facilities.

#### Equipment

81. (3.34) Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

82. (3.35) Repair and maintenance operations should not present any hazard to the quality of the products.

83. (3.36) Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition. It should be stored only in a clean and dry condition.

84. (3.37) Washing and cleaning equipment should be chosen and used so as not to be a source of contamination.

85. (3.38) Equipment should be installed in such a way as to prevent any risk of error or of contamination.

86. (3.39) Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will adversely affect the quality of the product and thus present any hazard.

87. (3.40) Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

88. (3.41) Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

89. (3.42) Fixed piping should be clearly marked to indicate the contents and, where applicable, the direction of flow.

90. (3.43) Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

91. (3.44) Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.

## DOCUMENTATION (CHAPTER 4)

### Principle

92. Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products. The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated

93. There are two primary types of documentation: used to manage and record GMP compliance: instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document.

94. Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term 'written' means recorded, or documented on media from which data may be rendered in a human readable form.

#### Documentation by type

95. Site Master File is a document describing the GMP related activities of the manufacturer.

96. Batch record is used to document the specific information for each individual batch, including release of approvals, and all quality-related factors.

97. Instructions (directions, or requirements) type:

Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation;

**Manufacturing Formulae, Processing, Packaging and Testing Instructions: Provide detail all the starting materials, equipment and computerised systems (if any) to be used and specify all processing, packaging, sampling and testing instructions. In-process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria;**

Procedures (otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations;

Protocols (plans) give instructions for performing and recording certain discreet operations (for example, validation protocols, validation plans);

Technical Agreements are agreed between contract givers and acceptors for outsourced activities.

98. Record/Report type:

Records: provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations. In the case of manufactured batches records should provide a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data;

Certificates of Analysis: Provide a summary of testing results on samples of products or materials together with the evaluation for compliance to a stated specification. In case if process analytical technology is used to manufacture a batch, compliance assessment may be based (in whole or in part) on the analysis of real-time data, parameters and result (summaries and deviation reports);

Reports: Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.

#### Generation and control of documentation

99. (4.1) All types of document should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Official copies should be maintained as determined by the manufacturer. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.

100 (4.2) Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorization dossiers. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

101. (4.3) Documents containing instructions should be approved, signed and dated by appropriate and authorized persons. Documents should have unambiguous contents. Documents should be uniquely identifiable. The effective date should be defined.

102. (4.4) Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use.

103. (4.5) Documents should be regularly reviewed and kept up-to-date.

104. (4.6) Documents should not be hand-written. Where documents require the entry of data, sufficient space should be provided for such entries.

#### Good Documentation Practices

105 (4.7) Handwritten entries should be made in clear, legible, indelible way.

106. (4.8) Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.

107. (4.9) Any alteration made to the entry on a document should be signed and dated. The alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

#### Retention of Documents

108. (4.10) It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period. Where appropriate, secure controls must be validated.

109. (4.11) Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Qualified Person, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.

110. (4.12) For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation should be retained whilst the authorization remains in force. It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise

## Specifications

111. (4.13) There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products.

### Specifications for starting and packaging materials

112 (4.14) Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:

a) (a) a description of the materials, including:

the designated name and the internal code reference;

the reference, if any, to a pharmacopoeial monograph, normative documentation or normative document;

the approved suppliers and, if reasonable, the original producer of the material;

a specimen of printed materials;

b) (b) directions for sampling and testing;

c) (c) qualitative and quantitative requirements with acceptance limits;

d) (d) storage conditions and precautions;

e) (e) the shelf-life.

### Specifications for intermediate and bulk products

113. (4.15) Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

### Specifications for finished products

114. (4.16) Specifications for finished products should include:

a) (a) the designated name of the product and the code reference where applicable;

b) (b) the formula or the appropriate reference to a pharmacopoeial monograph, normative documentation or a normative document;

c) (c) a description of the pharmaceutical form and package details;

d) (d) directions for sampling and testing or a reference to procedures;

e) (e) the qualitative and quantitative requirements, with the acceptance limits;

f) (f) the storage conditions and any special handling precautions, where applicable;

g) (g) the shelf-life.

### Manufacturing Formula and Processing Instructions

115. Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.

116. (4.17) The processing instructions should include a list of all starting materials to be used with the

amount of each, described, equipment to be used, description of production stages and control method at all stages of manufacture of medicinal products. General requirements and other requirements related to processing instructions are determined by appropriate normative regulation of the Russian Federation.

117. (4.18) The Processing Instructions should include:

- a) (a) an explanation of the processing location and the principal equipment to be used;
- b) (b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
- c) (c) checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;
- d) (d) detailed instructions relating to processing steps (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
- e) (e) the instructions for any in-process controls with their limits;
- f) (f) where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;
- g) (g) any special precautions to be observed.

#### Packaging Instructions

118. (4.19) Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:

- a) (a) name of the product; including the batch number of bulk and finished product;
- b) (b) description of its pharmaceutical form, and strength where applicable;
- c) (c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- d) (d) a complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
- e) (e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
- f) (f) checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use;
- g) (g) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- h) (h) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- i) (i) details of in-process controls with instructions for sampling and acceptance limits.

#### Batch Record

119. A batch record should be kept for each batch processed and packaged and include other documents confirming GMP compliance of each single batch, and distribution and release documents.

#### Batch Processing Records

120. (4.20) A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:

- a) (a) the name and batch number of the product;
- b) (b) dates and times of commencement, of significant intermediate stages and of completion of production;
- c) (c) identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
- d) (d) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- e) (e) any relevant processing operation or event and major equipment used;
- f) (f) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- g) (g) the product yield obtained at different and pertinent stages of manufacture;
- h) (h) notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
- i) (i) approval by the person responsible for the processing operations.

121. Batch processing records are documented simultaneously with the relevant processing operation.

122. Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception/ out-of-specification (OOS) data reports.

#### Batch Packaging Record

123. (4.21) A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions.

124. The batch packaging record should contain the following information:

- a) (a) the name and batch number of the product;
- b) (b) the date(s) and times of the packaging operations;
- c) (c) identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
- d) (d) records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;
- e) (e) details of the packaging operations carried out, including references to equipment and the packaging lines used;
- f) (f) samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- g) (g) notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;
- h) (h) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an

adequate reconciliation. Where there are there are robust electronic controls in place during packaging there may be justification for not including this information;

- i) (i) approval by the person responsible for the packaging operations.

#### Procedures and records

##### Receipt

125. (4.22) There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.

126. (4.23) The records of the receipts should include:

- a) (a) the name of the material on the delivery note and the containers;
- b) (b) the "in-house" name (if different from a hereto) and/or code of material (if applicable);
- c) (c) date of receipt;
- d) (d) supplier's name and, manufacturer's name;
- e) (e) manufacturer's batch or reference number;
- f) (f) total quantity and number of containers received;
- g) (g) the batch number assigned after receipt;
- h) (h) any relevant comment.

127. (4.24) There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

##### Sampling

128. (4.25) There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

##### Testing

129. (4.26) There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

##### Other

130. (4.27) Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Qualified Person(s). All records should be available to the Qualified Person. A system should be in place to indicate special observations and any changes to critical data.

131. (4.28) Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.

132. (4.29) There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

validation and qualification of processes, equipment and systems;



equipment assembly and calibration;

technology transfer;

maintenance, cleaning and sanitation;

personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training;

pest control;

complaints;

recalls;

returns;

change control;

investigations into deviations and non-conformances;

internal quality/GMP compliance audits;

summaries of records where appropriate (e.g. product quality review);

supplier audits.

133. (4.30) Clear operating procedures should be available for major items of manufacturing and test equipment.

134. (4.31) Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

(4.32) An inventory of documents within the Quality Management System should be maintained.

## PRODUCTION (CHAPTER 5)

### Principle

135. Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.

### General

136. (5.1) Production should be performed and supervised by competent people.

137. (5.2) All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

138. (5.3.) All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

139. (5.4) Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

140. (5.5) Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

141. (5.6) Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

142. (5.7) All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

143. (5.8) Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

144 (5.9) Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

145. (5.10) At every stage of processing, products and materials should be protected from microbial and other contamination.

146. (5.11) When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.

147. (5.12) At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

148. (5.13) Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status.

149. (5.14) Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

150. (5.15) Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control department when appropriate.

151. (5.16) Access to production premises should be restricted to authorised personnel.

152. (5.17) Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products.

#### Prevention of cross-contamination in production

153. (5.18) Contamination of a starting material or of a product by another material or product should be prevented. This risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapors, aerosols, genetic material or organisms from active substances, other starting materials, and products in process, from residues on equipment, and from operators' clothing should be assessed. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Amongst the most hazardous contaminants are highly sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

154. (5.19) Cross-contamination should be avoided by appropriate technical and (or) organizational measures, including:

a) (a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biological products), or by campaign (separation in time) followed by appropriate

cleaning;

b) (b) providing appropriate air-locks and air extraction;

c) (c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

d) (d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;

e) (e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

f) (f) using "closed systems" of production;

g) (g) testing for residues (of contamination) and use of cleaning status labels on equipment.

155. (5.20) Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

#### Validation

156. (5.21) Validations studies should support Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

156. (5.22) When any new manufacturing formula or method of preparation is adapted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

158. (5.23) Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

159. (5.24) Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

#### Starting materials

160. (5.25) The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.

161. (5.26) Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that the manufacturer and the supplier also discuss all aspects of the production and analysis of the starting material in question, including handling, labeling and packaging, as well as complaints and rejection procedures.

162. (5.27) For each delivery, the containers should be checked for integrity and closure (seal) of package and for correspondence between the delivery note and the supplier's labels.

163. (5.28) Where a delivery of materials is made up of different batches, each batch must be separately sampled, tested and authorized for release.

164. (5.29) Starting materials in the storage area should be appropriately labeled (see [section 148](#) hereto). Labels should bear at least the following information:

the designated name of the product and the internal code reference where applicable;

a batch number given at receipt;

where appropriate, the status of the product (e. g. in quarantine, on test, released, rejected);

where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.

165. (5.30) There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from whose batch samples have been drawn should be identified (see [section 216](#) hereto).

166. (5.31) Only starting materials which have been released by the quality control department and which are within their shelf life should be used.

167. (5.32) It should be ensured that starting materials are only dispensed by persons authorized for this purpose, following a written procedure so that the correct materials are accurately weighed or measured into clean and properly labeled containers.

168. (5.33) The weight or volume of each weighed material should be independently checked. The results should be recorded.

169. (5.34) Materials dispensed for each batch should be kept together and conspicuously labeled as such.

#### Processing operations: intermediate and bulk products

170. (5.35) Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

171. (5.36) Intermediate and bulk products should be kept under appropriate conditions.

172. (5.37) Critical processes should be validated (see [section 156 - 159](#) hereto).

173. (5.38) Any necessary in-process controls and environmental controls should be carried out and recorded.

174. (5.39) Any significant deviation from the expected yield should be recorded and investigated.

#### Packaging materials

175. (5.40) The purchase, handling and control of primary and printed packaging materials shall be accorded the same level of attention as that given to starting materials.

176. (5.41) Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

177. (5.42) Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

178. (5.43) Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

#### Packaging operations

179. (5.44) When setting up a program for the packaging operations, particular attention should be given to

minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

180. (5.45) Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used (unless these are to be used subsequently). The line-clearance should be performed according to an appropriate check-list.

181. (5.46) The name and batch number of the product being handled should be displayed at each packaging station or line.

182. (5.47) All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

183. (5.48) Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

184. (5.49) Normally, filling and sealing (coating) should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

185. (5.50) The correct performance of any printing operation, including for example code numbers and expiry dates, to be done separately or in the course of the packaging should be checked and recorded. Particular attention should be paid to printing by hand which should be re-checked at regular intervals.

186. (5.51) Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, as these help to avoid mix-ups.

187. (5.52) Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

188. (5.53) Printed and embossed information on packaging materials should be resistant to fading or erasing.

189. (5.54) On-line control of the product during packaging should include at least checking the following:

- a) (a) general appearance of the packages;
- b) (b) whether the packages are complete;
- c) (c) whether the correct products and packaging materials are used;
- d) (d) whether any over-printing is correct;
- e) (e) correct functioning of line monitors.

190. Samples taken away from the packaging line should not be returned.

191. (5.55) Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed record should be kept of this operation.

192. (5.56) Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

193. (5.57) Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A written procedure should be followed if uncoded printed materials are returned to stock.

#### Finished products

194. (5.58) Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

195. (5.59) The evaluation and documentation of finished products which is necessary before release of product for sale are described in [section 202 - 236](#) hereto.

196. (5.60) After release, finished products should be stored as usable stock under conditions established by the manufacturer.

#### Rejected, recovered and returned materials and products

197. (5.61) Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorized personnel.

198. (5.62) The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met. The reprocessing should be done in accordance with a defined and authorized procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

199. (5.63) The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved (including any effect on shelf life). The recovery should be recorded.

200. (5.64) The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the quality control department.

201. (5.65) Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory. They may be considered for re-sale, re-labeling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical re-processing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

### QUALITY CONTROL (CHAPTER 6)

#### Principle

202. Quality Control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control ([sections 5 - 23](#) hereto).

#### General

203. (6.1) Each manufacturing site should have a quality control department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out.

204. (6.2) The principal duties of the head of quality control are summarized in [sections 24 - 45](#) hereto. The quality control department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labeling of containers of materials and products, monitor stability of the products, participate in the investigation of complaints related to the quality of the product. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

205. (6.3) Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

Quality control personnel should have access to production areas for sampling and investigation as appropriate.

#### Good Quality Control Laboratory Practice

207. (6.5) Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in [sections 46 - 91](#) hereto.

208. (6.6) The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in [sections 237 - 255](#) hereto, can be accepted for particular reasons, but this should be stated in the Quality Control records.

#### Documentation

209. (6.7) Laboratory documentation should follow the principles given in [sections 92 - 134](#) hereto. An important part of this documentation deals with Quality Control.

The following details should be readily available to the Quality Control Department

specifications;

procedures describing sampling;

testing procedures and records (including analytical worksheets and/or laboratory notebooks);

analytical reports and/or certificates;

data from environmental monitoring, where required;

validation records of test methods, where applicable;

procedures for and records of the calibration of instruments and maintenance of equipment.

211. (6.8) Any quality control documentation relating to a batch record should be retained at least 5 years as stipulated in the Regulation on the Manufacturing Sites of Medicinal Products for Human Use, and for one year after the expiry date of the batch (as stipulated in [b, section 28](#) hereto).

212. (6.9) For some kinds of data (i.e. analytical tests results, yields, environmental controls) it is recommended that records are kept in a manner permitting trend evaluation.

213. (6.10) In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

#### Sampling

214. (6.11) The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required sub-division of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;

any special precautions to be observed, especially with regard to the sampling of sterile or health threatening materials;

- the storage conditions;
- instructions for the cleaning and storage of sampling equipment.

215. (6.12) Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most critical part of a process (e. g. at the beginning or end of a process).

216. (6.13) Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.

217. (6.14) Further guidance and additional information on shelf samples are given in [Annex No. 18](#) hereto.

#### Testing

218. (6.15) Analytical methods should be validated. All testing operations provided in the marketing authorization dossier should be carried out according to the approved methods.

219. (6.16) The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be meticulously examined.

220. (6.17) The tests performed should be recorded and the records should include at least the following data:

- a) (a) name of the material or product and, where applicable, dosage form;
- b) (b) batch number and, where appropriate, the manufacturer and/or supplier;
- c) (c) references to the relevant specifications and testing procedures;
- d) (d) test results, including observations and calculations, and reference to any certificates of analysis;
- e) (e) dates of testing;
- f) (f) initials of the persons who performed the testing;
- g) (g) initials of the persons who verified the tests and their results, where appropriate;

h) (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

221 (6.18) All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by quality control and the results recorded.

222. (6.19) Special attention should be given to the quality of laboratory reagents, volumetric glassware and



solutions, reference standards and culture media. These materials should be prepared in accordance with written procedures.

223. (6.20) Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

224. (6.21) Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

225. (6.22) Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. These animals should be maintained and controlled in a manner that assures their suitability for the intended use. The animals should be identified, and adequate records should be maintained, showing the history of their use.

#### On-going stability program

226. (6.23) After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate program that will permit the detection of any stability issue (e. g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.

227. (6.24) The purpose of the on-going stability program is to monitor the product over its shelf life and to determine that the product remains, and is expected to remain, within specifications under the labeled storage conditions.

228. (6.25) This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the program of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored for stability on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

229. (6.26) The on-going stability program should be described in a written protocol following the general rules specified in [sections 92 - 134](#) hereto and results formalized as a report. The equipment used for the on-going stability program (stability chambers among others) should be qualified and maintained following the general rules specified in [sections 46 - 91](#) and [Annex N 15](#) hereto.

230. (6.27) The protocol for an on-going stability program should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:

number of batches per activity and different batch sizes, if applicable;

relevant physical, chemical, microbiological and biological test methods;

acceptance criteria;

reference to test methods;

description of the container closure system(s);

testing intervals (time points);

description of the conditions of storage (standardized conditions for long term testing, consistent with the product labeling, should be used in accordance with normative regulations of the Russian Federation);

other applicable parameters specific to the medicinal product.

231. (6.28) The protocol for the on-going stability program can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example the frequency of testing).

232. (6.29) The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every activity and every primary packaging type, if relevant, should be included in the stability program unless none are produced during that year. For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

233. (6.30) In certain situations, additional batches should be included in the on-going stability program. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

234. (6.31) Results of on-going stability studies should be made available to main personnel and, in particular, to the responsible manager. Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, a written agreement must exist between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by executive bodies.

235. (6.32) Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the executive bodies. The possible impact on batches on the market should be evaluated in accordance with [sections 256- 272](#) hereto and in consultation with the executive bodies.

236. (6.33) A summary of all the data generated, including any interim conclusions on the program, should be written and maintained. This summary should be subjected to periodic review.

## OUTSOURCES ACTIVITIES (CHAPTER 7)

### Principle

237. Any activity stipulated by the GMP guidelines as well as outsourced activities must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility.

238. [Sections 237 - 255](#) hereto deal with the responsibilities of manufacturers towards the Competent Authorities with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of contract acceptors and contract givers to consumers; this is governed by other provisions of the Russian law.

### General

239. (7.1) There should be a written contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

240. (7.2) All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned.

241. (7.3). Where the marketing authorization holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this [sections 237 - 255](#) hereto.

#### The Contract Giver

242. (7.4) The pharmaceutical quality system of the Contract Giver, including the management responsibilities, extends to the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management.

243. (7.5) Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor (including, availability of licenses in accordance with the Russian law) to carry out successfully the outsourced activities and for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this Guide are followed. It is recommended to include provisions ensuring GMP compliance into the Contract.

244. (7.6) The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

245. (7.7) The Contract Giver should monitor and review of the performance of the contract acceptor and the identification and implementation of any needed improvement.

246. (7.8) The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He should also ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by a Qualified Person.

#### The Contract Acceptor

247. (7.9) The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.

248. (7.10) The Contract Acceptor should ensure that all products, materials and knowledge delivered to him are suitable for their intended purpose.

249. (7.11) The Contract Acceptor should not subcontract to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.

250. (7.12) The Contract Acceptor should not make unauthorized changes, which may adversely affect the quality of the outsourced activities for the contract giver.

251. (7.13) The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

#### The Contract

252. (7.14) A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and Marketing Authorization.

253. (7.15) The contract should describe clearly who is responsible for each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of

materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).

254. (7.16) All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.

255. (7.17) The contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or his mutually agreed subcontractor.

## COMPLAINTS AND PRODUCT RECALL (CHAPTER 8)

### Principle

256. All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. A system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

### Complaints

257. (8.1) A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the responsible manager, the responsible manager should be made aware of any complaint, investigation or recall.

258. (8.2) There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

259. (8.3) Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the study of such problems.

260. (8.4) If a product defect is discovered or suspected in a batch, a decision should be made to check other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

261. (8.5) All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

262. (8.6) Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

263. (8.7) Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

264. (8.8) The competent authorities should be informed if a manufacturer is considering action following possible faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product.

### Recalls

265. (8.9) A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls. This responsible person should normally be independent of the sales and marketing organization. If this person is not the responsible manager, the latter should be made aware of any recall operation.

266. (8.10) There should be established written procedures, regularly checked and updated when necessary, in order to organize any recall activity.

267. (8.11) Recall operations should be capable of being initiated promptly and at any time.

268. (8.12) All competent authorities of all countries to which products may possibly be distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.

269. (8.13) The distribution records should be readily available to the persons responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches, and amounts delivered), including those for exported products and medical samples.

270. (8.14) Recalled products should be identified and stored separately in a secure area while awaiting a decision on what is to be done of them.

271. (8.15) The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

272. (8.16) The effectiveness of the arrangements for recalls should be evaluated regularly.

## SELF INSPECTION (CHAPTER 9)

### Principle

273. Self Inspections should be conducted in order to monitor compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

274 (9.1) After preparation of a pre-arranged program, personnel matters, premises, equipment, documentation, production, quality control, market distribution of the pharmaceutical products, arrangements for dealing with complaints and recalls, and self inspection efforts, should be examined at intervals in order to verify their conformity with the principles of Quality Assurance.

275. (9-2) Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.

276. (9.3) All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where possible, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

## IV. BASIC REQUIREMENTS FOR ACTIVE SUBSTANCES USED AS STARTING MATERIALS (PART II)

### INTRODUCTION (1)

277. Manufacturing authorisation holders and manufacturers should only use active substances that have been manufactured in accordance with Good Manufacturing Practice for starting materials.

#### Objective (1.1)

278. These guidelines are intended to provide guidance regarding Good Manufacturing Practice for the manufacture of active substances under an appropriate system for managing quality. It is also intended to help ensure that active substances meet the requirements for quality and purity that they purport or are represented to possess.

279. In these guidelines "manufacturing" includes all operations with active substances: receipt of materials, production, packaging, repackaging, labeling, relabelling, quality control, release, storage and distribution of active substances and the related controls. The term "should" indicates recommendations that are expected to apply unless shown to be inapplicable, modified in any relevant annexes to the GMP Guide, or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

280. These guidelines are not intended to define registration requirements. These guidelines do not affect the ability of the responsible competent authority to establish specific registration requirements regarding active substances within the context of marketing/manufacturing authorizations.

#### Scope (1.2)

281. These guidelines apply to the manufacture of active substances for medicinal products for both human and veterinary use, including manufacture of active substances that are produced using blood or plasma as raw materials. They apply to all active starting materials described in the annexes to the GMP Guide, in particular [Annexes NN 2 - 7](#) where supplementary guidance for certain types of active substance may be found.

282. [Sections 622 - 644](#) hereto contain guidance that only applies to the manufacture of active substances used in the production of investigational medicinal products.

283. This chapter applies to the manufacture of sterile active substances only up to the point immediately prior to the active substance being rendered sterile.

284. The sterilisation and aseptic processing of sterile active substances are not covered by this chapter. This should be performed in accordance with the principles and guidelines of GMP as described in [Annex N 1](#) hereto, as well as with normative regulations of the Russian Federation.

285. These guidelines exclude, whole blood and plasma, as well as bulk-packaged medicinal products ("angro", "in bulk") as the detailed requirements for the collection and testing of blood are laid down by corresponding normative regulations of the Russian Federation. In case of ectoparasiticides for veterinary use, than standards stipulated by the Russian legislation, that ensure that the material is of appropriate quality, may be used.

286. An "Active Substance Starting Material" is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance. An Active Substance Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. Active Substance Starting Materials normally have defined chemical properties and structure.

287. The manufacturer should designate and document the rationale for the point at which production of the active substance begins. For synthetic processes, this is known as the point at which "Active Substance Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc), this rationale should be established on a case-by-case basis. [Table N 1](#) gives guidance on the point at which the Active Substance Starting Material is normally introduced into the process. From this point on, appropriate GMP as defined in these guidelines should be applied to these intermediate and/or active substance manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the active substance. However, it should be noted that the fact that a manufacturer chooses to validate a process step does not necessarily define that step as critical. The guidance in this document would normally be applied to the steps shown in grey in [Table N 1](#). It does not imply that all steps shown in this [table](#) should be completed. The stringency of GMP in active substance manufacturing should increase as the process proceeds from early steps to final steps, purification, and packaging. Physical processing of active substances, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronising), should be conducted at least to the standards of these guidelines. These guidelines do not apply to steps prior to the first introduction of the defined "Active Substance Starting Material".

288. In the remainder of this guideline the term Active Pharmaceutical Ingredient (API) is used repeatedly and should be considered interchangeable with the term "Active Substance". The glossary used in this Chapter (in [section 645](#) hereto) should only be applied in the context of this Chapter.

Table N 1. Application of [Chapter IV](#) to API Manufacturing

Тип   Стадии производства ФС, на которые распространяется <a href="#">глава IV</a>   производства   настоящих Правил (выделены серым фоном)		
<b>ConsultantPlus</b> reliable legal support	<a href="http://www.consultant.ru">www.consultant.ru</a>	Page 38 of 178

Химическое производство   Введение в производство   Выделение   Обработка   производство   исходного сырья   процесс   промежуточного   и очистка   физическими   для ФС   исходного   продукта (ов)   методами и   сырья для   упаковка   производства   ФС
ФС, получаемые из сырья   Сбор органов, жидкостей или тканей и (или) происхождения   первичная обработка   Реска, смешивание   исходного сырья для производства   Введение в процесс   и очистка   физическими   методами и   упаковка   Выделение   Обработка
ФС, получаемые из сырья   первичная обработка   Реска и   Введение в процесс   и очистка   физическими   растительного происхождения   экстракция   исходного сырья для производства   методами и   упаковка   Выделение   Обработка
Растительные экстракты, используемые в Packaging   Сбор растений   первичная обработка   Реска и   экстракция   физическими   -   Дальнейшая   Обработка   методами и
ФС, состоящие из   (или)   (или)   физическими   размельченных   культивирование   измельчение   методами и   или растертых в порошок   и сбор   упаковка   растений
Биотехнология: ферментация и (или) культивирование клеток   Создание   Поддержание   Культивирование   Выделение   Обработка   главного и   рабочего   клеток и (или)   и очистка   физическими   (или)   рабочего   банка   банка   ферментация   методами и   культивирование   клеток   упаковка
"Классическая" ферментация для производства ФС   Создание   Поддержание   Ввод клеток в   Выделение   Обработка   банка   банка   процесс   и очистка   физическими   ферментации   методами и   упаковка
Усиление требований \ /

## QUALITY MANAGEMENT (2)

### Principles (2.1)

289. (2.10) Quality should be the responsibility of all persons involved in manufacturing.

290. (2.11) Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

291. (2.12) The system for managing quality should encompass the organizational structure, procedures,

processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.

292. (2.13) There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

293. (2.14) The persons authorized to release intermediates and APIs should be specified.

294. (2.15) All quality related activities should be recorded at the time they are performed.

295. (2.16) Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

296. (2.17) No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in [section 472](#) hereto or the use of raw materials or intermediates pending completion of evaluation).

297. (2.18) Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).

298. (2.19) To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented quality system incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management.

#### Quality Risk Management (2.2)

299. (2.20) Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the active substance. It can be applied both proactively and retrospectively.

300. (2.21) The quality risk management system should ensure that:

the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient through communication with the user of the active substance;

the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

#### Responsibilities of the Quality Unit(s) (2.3)

301. (2.30) The quality unit(s) should be involved in all quality-related matters.

302. (2.31) The quality unit(s) should review and approve all appropriate quality-related documents.

303. (2.32) The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:

a) (1) Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;

b) (2) Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;

c) (3) Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;

d) (4) Making sure that critical deviations are investigated and resolved;



- e) (5) Approving all specifications and master production instructions;
- f) (6) Approving all procedures impacting the quality of intermediates or APIs;
- g) (7) Making sure that internal audits (self-inspections) are performed;
- h) (8) Approving intermediate and API contract manufacturers;
- i) (9) Approving changes that potentially impact intermediate or API quality;
- j) (10) Reviewing and approving validation protocols and reports;
- k) (11) Making sure that quality related complaints are investigated and resolved;
- l) (12) Making sure that effective systems are used for maintaining and calibrating critical equipment;
- m) (13) Making sure that materials are appropriately tested and the results are reported;
- n) (14) Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate;
- o) (15) Performing product quality reviews (as defined in [sections 307 - 308](#) hereto).

#### Responsibility for Production Activities (2.4)

304. The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

- a) (1) Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;
- b) (2) Producing APIs and, when appropriate, intermediates according to pre approved instructions;
- c) (3) Reviewing all production batch records and ensuring that these are completed and signed;
- d) (4) Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;
- e) (5) Making sure that production facilities are clean and when appropriate disinfected;
- f) (6) Making sure that the necessary calibrations are performed and records kept;
- g) (7) Making sure that the premises and equipment are maintained and records kept;
- h) (8) Making sure that validation protocols and reports are reviewed and approved;
- i) (9) Evaluating proposed changes in product, process or equipment;
- j) (10) Making sure that new and, when appropriate, modified facilities and equipment are qualified.

#### Internal Audits (Self Inspection) (2.5)

305. (2.50) In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

305. (2.51) Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

## Product Quality Review (2.5)

307. (2.60) Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually. They should include at least:

- a review of critical in-process control and critical API test results;
- a review of all batches that failed to meet established specification(s);
- a review of all critical deviations or non-conformances and related investigations;
- a review of any changes carried out to the processes or analytical methods;
- a review of results of the stability monitoring program;
- a review of all quality-related returns, complaints and recalls;
- a review of adequacy of corrective actions.

308. (2.61) The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

## PERSONNEL (3)

### Personnel Qualifications (3.1)

309. (3.10) There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

310. (3.11) The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

311. (3.12) Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

### Personnel Hygiene (3.2)

312. (3.20) Personnel should practice good sanitation and health habits.

313. (3.21) Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

314. (3.22) Personnel should avoid direct contact with intermediates or APIs.

315. (3.23) Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

316. (3.24) Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

### Consultants (3.3)

317. (3.30) Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

318. (3.31) Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

## BUILDINGS AND FACILITIES (4)

### Design and Construction (4.1)

319. (4.10) Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

320. (4.11) Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

321. (4.12) Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

322. (4.13) The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

323. (4.14) There should be defined areas or other control systems for the following activities:

receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;

quarantine before release or rejection of intermediates and APIs;

sampling of intermediates and APIs;

holding rejected materials before further disposition (e.g., return, reprocessing or destruction);

storage of released materials;

production operations;

packaging and labelling operations;

laboratory operations.

324. (4.15) Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

325. (4.16) Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

### Utilities (4.2)

326. (4.20) All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating,

ventilation and air conditioning) should be qualified. They should be appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

327. (4.21) Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination. They should also include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

328. (4.22) If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

329. (4.23) Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

330. (4.24) Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

#### Water (4.3)

331. (4.30) Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use. The quality unit(s) must confirm compliance of this provision.

332. (4.31) The process water should, at a minimum, meet normative regulations of the Russian Federation for drinking (potable) water quality.

333. (4.32) If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

334. (4.33) Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

335. (4.34) Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

#### Containment (4.4)

336. (4.40) Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

337. (4.41) Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

338. (4.42) Appropriate measures should be established and implemented to prevent crosscontamination from personnel, materials, etc. moving from one dedicated area to another.

339. (4.43) Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

#### Lighting (4.5)

340. (4.50) Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

#### Sewage and refuse (4.6)

341. (4.60) Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

#### Sanitation and Maintenance (4.7)

342. (4.70) Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

343. (4.71) Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

344. (4.72) When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.

### PROCESS EQUIPMENT (5)

#### Design and Construction (5.1)

345. (5.10) Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

346. (5.11) Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

347. (5.12) Production equipment should only be used within its qualified operating range.

348. (5.13) Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

349. (5.14) Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

350. (5.15) Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

351. (5.16) A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

#### Equipment Maintenance and Cleaning

352. (5.20) Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

353. (5.21) Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

assignment of responsibility for cleaning of equipment;

cleaning schedules, including, where appropriate, sanitizing schedules;

a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;

when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;

instructions for the removal or obliteration of previous batch identification;

instructions for the protection of clean equipment from contamination prior to use;

inspection of equipment for cleanliness immediately before use, if practical;

establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

3.54 (5.22) Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilised to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

355. (5.23) Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

356. (5.24) Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

357. (5.25) Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

358. (5.26) Equipment should be identified as to its contents and its cleanliness status by appropriate means.

#### Calibration (5.3)

359. (5.30) Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

360. (5.31) Equipment calibrations should be performed using standards traceable to certified standards, if existing.

361. (5.32) Records of these calibrations should be maintained.

362. (5.33) The current calibration status of critical equipment should be known and verifiable.

363. (5.34) Instruments that do not meet calibration criteria should not be used.

364. (5.35) Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

#### computerised Systems (5.4)

365. (5.40) GMP related computerised systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application.

366. (5.41) Appropriate installation qualification and operational qualification should demonstrate the

suitability of computer hardware and software to perform assigned tasks.

367. (5.42) Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

368. (5.43) computerised systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

369. (5.44) Written procedures should be available for the operation and maintenance of computerised systems.

370. (5.45) Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

371. (5.46) Incidents related to computerised systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

372. (5.47) Changes to the computerised system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

373. (5.48) If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerised systems.

374. (5.49) **Data can be recorded by a second means in addition to the computer system.**

## DOCUMENTATION AND RECORDS (6)

### Documentation System and Specifications (6.1)

375. (6.10) All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

376. (6.11) The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

377. (6.12) A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

378. (6.13) All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

379. (6.14) When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed. Such corrections should leave the original entry still readable.

380. (6.15) During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

381. (6.16) Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where

reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

382. (6.17) Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

383. (6.18) If electronic signatures are used on documents, they should be authenticated and secure.

#### Equipment Cleaning and Use Record (6.2)

384. (6.20) Records of major equipment use, cleaning, sanitization and/or sterilisation and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

385. (6.21) If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

#### Records of Raw Materials, Intermediates, API Labelling and Packaging Materials (6.3)

386. (6.30) Records of raw materials, intermediates, API labelling and packaging materials should be maintained including:

the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs;

the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;

the results of any test or examination performed and the conclusions derived from this;

records tracing the use of materials;

documentation of the examination and review of API labelling and packaging materials for conformity with established specifications;

the final decision regarding rejected raw materials, intermediates or API labeling and packaging materials.

387. (6.31) Master (approved) labels should be maintained for comparison to issued labels.

#### Master Production Instructions (6.4)

388. (6.40) To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s). Master production instructions are developed based on the processing instructions for each production stage and intermediate, and should be signed and dated by one person and independently checked, dated, and signed by a person in the quality unit(s). The processing instructions should include a list of all starting materials to be used with the amount of each, described, equipment to be used, description of production stages and control method at all stages of manufacture of medicinal products. General requirements and other requirements related to processing instructions are determined by appropriate normative regulation of the Russian Federation.



389. (6.41) Master production instructions should include:

the name of the intermediate or API being manufactured and an identifying document reference code, if applicable;

a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;

an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;

the production location and major production equipment to be used;

detailed production instructions, including the:

sequences to be followed;

ranges of process parameters to be used;

sampling instructions and in-process controls with their acceptance criteria, where appropriate;

time limits for completion of individual processing steps and/or the total process, where appropriate;

expected yield ranges at appropriate phases of processing or time;

where appropriate, special notations and precautions to be followed, or cross references to these;

the instructions for storage of the intermediate or API to assure its suitability for use, including the labeling and packaging materials and special storage conditions with time limits, where appropriate.

#### Batch Production Records (Batch Production and Control Records) (6.5)

390. (6.50) Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

391. (6.51) These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

392. (6.52) Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

dates and, when appropriate, times;

identity of major equipment (e.g., reactors, driers, mills, etc.) used;

specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;

actual results recorded for critical process parameters;

any sampling performed;

- signatures of the persons performing and directly supervising or checking each critical step in the operation;
- in-process and laboratory test results;
- actual yield at appropriate phases or times;
- description of packaging and label for intermediate or API;
- representative label of API or intermediate if made commercially available;
- any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately;
- results of release testing.

393. (6.53) Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

#### Laboratory Control Records (6.6)

394. (6.60) Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, normative documentation or normative documents, including examinations and assays, as follows:

- a description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;

- a statement of or reference to each test method used;

- a statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;

- a complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;

- a record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;

- a statement of the test results and how they compare with established acceptance criteria;

- the signature of the person who performed each test and the date(s) the tests were performed;

- the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

395. (6.61) Complete records should also be maintained for:

- any modifications to an established analytical method;

- periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;

- all stability testing performed on APIs;

- out-of-specification investigations.

#### Batch Production Record Review (6.7)

396. (6.70) Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

397. (6.71) Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

398. (6.72) All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

399. (6.73) The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

## MATERIALS MANAGEMENT (7)

### General Controls (7.1)

400. (7.10) There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

401. (7.11) Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

402. (7.12) Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).

403. (7.13) If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

404. (7.14) Changing the source of supply of critical raw materials should be treated according to [sections 540 - 547](#) hereto.

### Receipt and Quarantine (7.2)

405. (7.20) Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.

406. (7.21) Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

407. (7.22) If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

certificate of cleaning;

testing for trace impurities;

audit of the supplier;

408. (7.23) Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

409. (7.24) Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

#### Sampling and Testing of Incoming Production Materials (7.3)

410. (7.30) At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described in [section 412](#) hereto. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

411. (7.31) Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

412. (7.32) Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

413. (7.33) Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

414. (7.34) Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

415. (7.35) Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

#### Storage (7.4)

416. (7.40) Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

417. (7.41) Materials stored in fiber drums, bags, or boxes should be stored off the floor. When appropriate, materials should be suitably spaced to permit cleaning and inspection.

418. (7.42) Materials should be stored under conditions and for a period that have no adverse affect on their quality. Materials should normally be controlled so that the oldest stock is used first.

419. (7.43) Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

420. (7.44) Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.

#### Re-evaluation (7.5)

421. (7.50) Materials should be re-evaluated as appropriate to determine their suitability for use (e. g., after prolonged storage or exposure to heat or humidity).

### PRODUCTION AND IN-PROCESS CONTROLS

(8)

### Production Operations (8.1)

422. (8.10) Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

423. (8.11) If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

material name and/or item code;

receiving or control number;

weight or measure of material in the new container;

re-evaluation or retest date if appropriate.

424. (8.12) Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

425. (8.13) Other critical activities should be witnessed or subjected to an equivalent control.

426. (8.14) Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

427. (8.15) Any deviation should be documented and explained. Any critical deviation should be investigated.

428. (8.16) The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

429. (8.17) Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

### Time Limits (8.2)

430. (8.20) If time limits are specified in the master production instruction (see [section 389](#) hereto), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

431. (8.21) Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

### In-process Sampling and Controls (8.3)

432. (8.30) Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

433. (8.31) The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which

the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

434. (8.32) Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

435. (8.33) In-process controls can be performed by qualified production department personnel. The process can be adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

436. (8.34) Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

437. (8.35) In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

438. (8.36) Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

#### Blending Batches of Intermediates or APIs (8.4)

439. (8.40) For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

440. (8.41) Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

441. (8.42) Acceptable blending operations include but are not limited to:

blending of small batches to increase batch size;

blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

442. (8.43) Blending processes should be adequately controlled and documented. The blended batch should be tested for conformance to established specifications where appropriate.

443. (8.44) The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

444. (8.45) Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

445. (8.46) If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

446. (8.47) The expiry or retest date of the blended batch should be based on the manufacturing date of the

oldest tailings or batch in the blend.

#### Contamination Control (8.5)

447. (8.50) Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

448. (8.51) Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

449. (8.52) Precautions to avoid contamination should be taken when APIs are handled after purification.

### PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES (9)

#### General (9.1)

450. (9.10) There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials.

451. (9.11) Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

452. (9.12) Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

#### Packaging Materials (9.2)

453. (9.20) Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

454. (9.21) Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

455. (9.22) If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

#### Label Issuance and Control (9.3)

456. (9.30) Access to the label storage areas should be limited to authorized personnel.

457. (9.31) Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

458. (9.32) All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

459. (9.33) Obsolete and out-dated labels should be destroyed.

460. (9.34) Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

461. (9.35) Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

462. (9.36) A printed label representative of those used should be included in the batch production record.

#### Packaging and Labeling Operations (9.4)

463. (9.40) There should be documented procedures designed to ensure that correct packaging materials and labels are used.

464. (9.41) Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

465. (9.42) Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.

466. (9.43) If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

467. (9.44) Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

468. (9.45) Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

469. (9.46) Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

### STORAGE AND DISTRIBUTION (10)

#### Warehousing Procedures (10.1)

470. (10.10) Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

471. (10.11) Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

#### Distribution Procedures (10.2)

472. (10.20) APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

473. (10.21) APIs and intermediates should be transported in a manner that does not adversely affect their quality.



474. (10.22) Special transport or storage conditions for an API or intermediate should be stated on the label.

475. (10.23) The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

476. (10.24) A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

## LABORATORY CONTROLS (11)

### General Controls (11.1)

477. (11.10) The independent quality unit(s) should have at its disposal adequate laboratory facilities and equipment.

478. (11.11) There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with [sections 394 - 395](#) hereto.

479. (11.12) All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

480. (11.13) Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

481. (11.14) Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.

482. (11.15) Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any re-sampling and/or retesting after OOS results should be performed according to a documented procedure.

483. (11.16) Reagents and standard solutions should be prepared and labelled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.

484. (11.17) Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

485. (11.18) Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

486. (11.19) Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be

periodically requalified in accordance with a written protocol.

#### Testing of Intermediates and APIs (11.2)

487. (11.20) For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

488. (11.21) An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin.

489. (11.22) The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

490. (11.23) Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

#### Validation of Analytical Procedures (11.3)

491. Validation of analytical procedures should be performed in accordance with [sections 511 - 539](#) hereto.

#### Certificates of Analysis (11.4)

492. (11.40) Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.

493. (11.43) Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

494 (11.42) The Certificate should list each test performed in accordance with compendia or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical) conducted in accordance with general pharmacopoeia, pharmacopoeia, normative documentation or normative documents.

495. (11.43) Certificates should be dated and signed by authorised personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address and telephone number of the repacker/ reprocessor and a reference to the name of the original manufacturer

496. (11.44) If new Certificates are issued by or on behalf of repackers/ reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

#### Stability Monitoring of APIs (11.5)

497. (11.50) A documented, on-going testing program should be designed to monitor the stability characteristics of APIs. The results should be used to confirm appropriate storage conditions and retest or expiry dates.

498. (11.51) The test procedures used in stability testing should be validated and be stability indicating.

499. (11.52) Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.

500. (11.53) Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

501. (11.54) Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

502. (11.55) For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. 9 month testing) can be considered.

503. (11.56) Where appropriate, the stability storage conditions should be consistent with the ICH guidelines "On stability testing of new drug substances and products" (ICH Q1A).

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<\*> For reference: The ICH Guidelines "On stability testing of new drug substances and products" (ICH Q1A) is available online: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Quality/Q1A\\_R2/Step4/Q1A\\_R2\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2_Guideline.pdf)

#### Expiry and Retest Dating (11.6)

504. (11.60) When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).

505. (11.61) An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

506. (11.62) Preliminary API expiry or retest dates can be based on pilot scale batches if: 1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and 2) the quality of the API represents the material to be made on a commercial scale.

507. (11.63) A representative sample should be taken for the purpose of performing a retest.

#### Reserve/Retention Samples (11.7)

508. (11.70) The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

509. (11.71) Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.

510. (11.72) The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses in accordance with normative documentation or a normative document.

## VALIDATION (12)

### Validation Policy (12.1)

511. (12.10) The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, inprocess control test procedures, computerised systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

512. (12.11) The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

defining the API in terms of its critical product attributes;

identifying process parameters that could affect the critical quality attributes of the API;

determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

513. (12.12) Validation should extend to those operations determined to be critical to the quality and purity of the API.

### Validation Documentation (12.2)

514. (12.20) A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

515. (12.21) The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e. g. retrospective, prospective, concurrent) and the number of process runs.

516. (12.22) A validation report that cross-references the validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

517. (12.23) Any variations from the validation protocol should be documented with appropriate justification.

### Qualification (12.3)

518. (12.30) Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

**Design Qualification:** documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

**Installation Qualification:** documented verification that the facilities, equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.

**Operation Qualification:** documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

**Performance Qualification:** documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

### Approaches to Process Validation (12.4)

519. (12.40) Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes. The result of process validation should be recorded.

520. (12.41) There are three approaches to validation: prospective validation, concurrent validation and retrospective validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used.

521. (12.42) Prospective validation should normally be performed for all API processes as defined in [section 513](#) hereto. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

522. (12.43) Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

523. (12.44) An exception can be made for retrospective validation for well established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

- a) (1) critical quality attributes and critical process parameters have been identified;
- b) (2) appropriate in-process acceptance criteria and controls have been established;
- c) (3) there have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability;
- d) (4) impurity profiles have been established for the existing API.

524. (12.45) Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications. They should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

#### Process Validation Program (12.5)

525. (12.50) The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide. But there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from 10-30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

526. (12.51) Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

527. (12.52) Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

#### Periodic Review of Validated Systems (12.6)

528. (12.60) Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review

confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

#### Cleaning Validation (12.7)

529. (12.70) Cleaning procedures should normally be validated. In general, cleaning validations should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

530. (12.71) Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

531. (12.72) The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.

532. (12.73) Sampling should include swabbing, rinsing, or alternative methods (e. g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e. g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

533. (12.74) Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

534. (12.75) Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

535. (12.76) Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

#### Validation of Analytical Methods (12.8)

536. (12.80) Analytical methods should be validated. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

537. (12.81) Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

538. (12.82) Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

539. (12.83) Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification

produces results that are as accurate and reliable as the established method.

### CHANGE CONTROL (13)

540. (13.10) A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

541. (13.11) Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.

542. (13.12) Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organisational units, and reviewed and approved by the quality unit(s).

543. (13.13) The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

544. (13.14) When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

545. (13.15) After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

546. (13.16) The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

547. (13.17) Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

### REJECTION AND RE-USE OF MATERIALS (14)

#### Rejection (14.1)

548. (14.10) Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked. The final disposition of rejected materials should be recorded.

#### Reprocessing (14.2)

549. (14.20) Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

550. (14.21) Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

551. (14.22) Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of byproducts and over-reacted materials.

### Reworking (14.3)

552. (14.30) Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.

553. (14.31) Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

554. (14.32) Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

### Recovery of Materials and Solvents (14.4)

555. (14.40) Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

556. (14.41) Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.

557. (14.42) Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

558. (14.43) The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

### Returns (14.5)

559. (14.50) Returned intermediates or APIs should be identified as such and quarantined.

560. (14.51) If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

561. (14.52) Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- name and address of the consignee;
- intermediate or API, batch number, and quantity returned;
- reason for return;
- use or disposal of the returned intermediate or API.

### COMPLAINTS AND RECALLS (15)

562. (15.10) All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

563. (15.11) Complaint records should include:



name and address of complainant;  
name (and, where appropriate, title) and phone number of person submitting the complaint;  
complaint nature (including name and batch number of the API);  
date complaint is received;  
action initially taken (including dates and identity of person taking the action);  
any follow-up action taken;  
response provided to the originator of complaint (including date response sent);  
final decision on intermediate or API batch or lot.

564. (15.12) Records of complaints should be retained in order to evaluate trends, product related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

565. (15.13) There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

566. (15.14) The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

567. (15.15) In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

#### CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) (16)

568. (16.10) All contract manufacturers (including laboratories) should comply with the GMP. Special consideration should be given to the prevention of crosscontamination and to maintaining traceability.

569. (16.11) Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.

570. (16.12) There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

571. (16.13) The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

572. (16.14) Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.

573. (16.15) Manufacturing and laboratory records should be kept at the site where the activity occurs. Such records should and be readily available.

574. (16.16) Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

#### REPACKERS AND RELABELERS (17)

Applicability (17.1)

575. (17.10) [Sections 575 - 589](#) apply to any party other than the original manufacturer who may repack and (or) relabel API or intermediate.

576. (17.11) All repackers, and relabellers should comply with GMP as defined in this Chapter.

#### Traceability of Distributed APIs and Intermediates (17.2)

577. (17.20) Repackers and (or) relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

- identity of original manufacturer;
- address of original manufacturer;
- purchase orders;
- bills of lading (transportation documentation);
- receipt documents;
- name or designation of API or intermediate;
- manufacturer's batch number;
- transportation and distribution records;

all authentic Certificates of Analysis, including certificates of quality received after repackaging and/or relabeling, including those of the original manufacturer;

retest or expiry date.

#### Quality Management (17.3)

578. (17.30) Repackers, or relabellers should establish, document and implement an effective system of managing quality, as specified in [sections 289 - 308](#) hereto.

#### Repackaging, Relabelling and Holding of APIs and Intermediates (17.4)

579. (17.40) Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of API or intermediate identity or purity.

580. (17.41) Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

#### Stability (17.5)

581. (17.50) Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

#### Transfer of Information (17.6)

582. (17.60) Repackers, or relabellers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

583. (17.61) Repackers and (or) relabellers who supply the API or intermediate to the customer should

provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

584. (17.62) Repackers and (or) relabellers should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents.

585. (17.63) The specific guidance for Certificates of Analysis included in [sections 492- 496](#) hereto should be met.

#### Handling of Complaints and Recalls (17.7)

586. (17.70) Repackers and (or) relabellers should maintain records of complaints and recalls, as specified in [sections 562 - 567](#) hereto, for all complaints and recalls that come to their attention.

587. (17.71) If the situation warrants, the repackers, or relabellers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

588. (17.2) Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the repackers, or relabellers should include any response received from the original API or intermediate manufacturer (including date and information provided).

#### Handling of Returns (17.8)

589. (17.80) Returns should be handled as specified in [section 561](#) hereto. The repackers and (or) relabellers should maintain documentation of returned APIs and intermediates.

### SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE OR FERMENTATION (18)

#### General (18.1)

590. (18.10) Sections 590 - [621](#) hereto are intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms. It is not intended to be a stand-alone Section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

591. (18.11) The term "biotechnological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in [sections 590 - 621](#) hereto. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

592. (18.12) The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

593. (18.13) Production of APIs or intermediates from cell culture or fermentation involves biological

processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

594. (18.14) Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this Guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This Chapter covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

595. (18.15) Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

596. (18.16) In general, process controls should take into account:

maintenance of the working cell bank (where appropriate);

proper inoculation and expansion of the culture;

control of the critical operating parameters during fermentation/cell culture;

monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;

harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;

monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production;

viral safety concerns.

597. (18.17) Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

#### Cell Bank Maintenance and Record Keeping (18.2)

598. (18.20) Access to cell banks should be limited to authorized personnel.

599. (18.21) Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

600. (18.22) Records of the use of the vials from the cell banks and storage conditions should be maintained.

601. (18.23) Where appropriate, cell banks should be periodically monitored to determine suitability for use.

602. (18.24) Special provisions related to maintenance of cell banks stipulated by the normative regulations of the Russian Federation should be followed.

#### Cell Culture and Fermentation (18.3)

603. (18.30) Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

604. (18.31) Where the quality of the API can be affected by microbial contamination, manipulations using

open vessels should be performed in a biosafety cabinet or similarly controlled environment.

605. (18.32) Personnel should be appropriately gowned and take special precautions handling the cultures.

606. (18.33) Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

607. (18.34) Cell culture equipment should be cleaned and sterilised after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilised.

608. (18.35) Culture media should be sterilised before use when appropriate to protect the quality of the API.

609. (18.36) There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches.

610. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

611. (18.37) Records of contamination events should be maintained.

612. (18.38) Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

#### Harvesting, Isolation and Purification (18.4)

613. (18.40) Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

614. (18.41) Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

615. (18.42) All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

616. (18.43) If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

617. (18.44) Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

#### Viral Removal/Inactivation steps (18.5)

618. (18.50) If otherwise not provided, special provisions of the Russian Federation related to viral removal and inactivation steps should be maintained.

619. (18.51) Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

620. (18.52) Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

621. (18.53) The same equipment is not normally used for different purification steps. However, if the same

equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

## APIs FOR USE IN CLINICAL TRIALS (19)

### General (19.1)

622. (19.10) Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new API for investigational use during its development. [Sections 622 - 644](#) hereto provide specific guidance unique to these circumstances.

623. (19.11) The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

### Quality (19.2)

624. (19.20) Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.

625. (19.21) A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

626. (19.22) Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

627. (19.23) Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

628. (19.24) Process and quality problems should be evaluated.

629. (19.25) Labelling for APIs intended for use in clinical trials should be appropriately controlled. It should identify the material as being for investigational use.

### Equipment and Facilities (19.3)

630. (19.30). During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

631. (19.31) Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

### Control of Raw Materials (19.4)

632. (19.40) Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis. Raw materials should be subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

633. (19.41) In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i. e., use testing) rather than on analytical testing alone.

#### Production (19.5)

634. (19.50) The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

635. (19.51) Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

#### Validation (19.6)

636. (19.60) Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.

637. (19.61) Process validation should be conducted in accordance with [sections 511 - 539](#) hereto when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

#### Changes (19.7)

638. (19.70) Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

#### Laboratory Controls (19.8)

639. (19.80) While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

640. (19.81) A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

641. (19.82) Expiry and retest dating as defined in [sections 504- 507](#) hereto applies to existing APIs used in clinical trials. For new APIs, [sections 504 - 507](#) hereto does not normally apply in early stages of clinical trials.

#### Documentation (19.9)

642. (19.90) A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

643. (19.91) The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

644. (19.92) A system for retaining production and control records and documents should be developed and used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

#### GLOSSARY (20)

145. For the purposes of this Annex, the following basic concepts are also used, in addition to the terms and definitions provided for in [Chapter II](#) hereto:

bioburden - the level and type (for example, objectionable or not) of microorganisms that may be present in the starting materials; starting materials for the production of a pharmaceutical substance, intermediates or in a pharmaceutical substance. Regarded as a contamination when its level exceeds the established limit values, or microorganisms identified as objectionable are detected;

process aids - materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc);

yield, expected - the quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data;

yield, theoretical - the quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production;

expiry date - the date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used;

retest date - the date when a material should be re-examined to ensure that it is still suitable for use;

Starting materials for active substances are raw materials, intermediates or other active substances used to produce active substances and are used as significant structural fragment in the structure of active substances. Starting material for manufacture of active substances can be purchased from one or more suppliers under contract, or produced in-house. Active substance starting materials normally have defined chemical properties and structure.

computerised system- a group of hardware components and associated software, designed and assembled to perform a specific function or group of functions;

contamination - the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport;

acceptance criteria - numerical limits, ranges, or other suitable measures for acceptance of test results;

critical - a term which describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification;

material - a general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials;

mother liquor - the residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

quality assurance - the sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained;

deviation - departure from an approved instruction or established standard;

reworking - subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent);

signature (signed) - the record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature;

quality unit(s) - an organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization;

impurity - any component present in the intermediate or API that is not the desired entity;



contract manufacturer - a manufacturer performing some aspect of manufacturing on behalf of the original manufacturer;

validation protocol - a written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results;

impurity profile - a description of the identified and unidentified impurities present in an API;

solvent - an inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API;

reference standard, secondary - a substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis;

reference standard, primary - a substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material;

active pharmaceutical ingredients (API) - medicines in the form of active substances of biological, biotechnological, mineral or chemical origin, being pharmacologically active, meant for manufacturing and compounding of medicinal products and determining efficacy thereof.

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Paragraph 2, Article 4, Federal Law No. 61-FZ of 12.04.2010 "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Art. No.1815)

Annex No. 1  
to Good Manufacturing  
Practice

## MANUFACTURE OF STERILE MEDICINAL PRODUCTS

### I. PRINCIPLE

1. The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

2. The detailed methods for determining the microbiological and particulate cleanliness of air, surfaces etc. are determined by the normative regulations of the Russian Federation.

### II. GENERAL

3. (1.) The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

4. (2) The various operations of component preparation, product preparation and filling should be carried out

in separate areas within the clean area. Manufacturing operations are divided into two categories: firstly those where the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.

5. (3) Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.

6. In order to meet "in operation" conditions these areas should be designed to reach certain specified air-cleanliness levels in the "at rest" occupancy state.

7. The "at-rest" state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present.

8. The "in operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

9. The "in operation" and "at rest" states should be defined for each clean room or suite of clean rooms.

10. For the manufacture of sterile medicinal products 4 grades can be distinguished:

Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes;

Grade B: For aseptic preparation and filling, this is the background environment for the grade A zone;

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

### III. CLEAN ROOM AND CLEAN AIR DEVICE CLASSIFICATION

11. (4) Clean rooms and clean air devices should be classified Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in table N 1.

<\*> For reference: GOST R ISO 14644-1 (EN ISO 14644-1).

Table N 1

Grade	Maximum permitted number of particles per 1m <sup>3</sup> equal to or greater than the tabulated size			
	At rest		In operation	
	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352,000	2 900
C	352,000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

12. (5) For classification purposes in Grade A zones, a minimum sample volume of 1m<sup>3</sup> should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles  $\geq 5.0 \mu\text{m}$ .

For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes.

For Grade C (at rest & in operation) the airborne particle classification is ISO 7 and ISO 8 respectively.

For Grade D (at rest) the airborne particle classification is ISO 8.

For classification purposes <\*> methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.

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<\*> For reference: GOST R ISO 14644-1 (EN ISO 14644-1).

13. (6) Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles  $\geq 5.0 \mu\text{m}$  in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems.

14. (7) "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this.

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<\*> For reference: GOST R ISO 14644-2 (EN ISO 14644-2) provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

#### IV. CLEAN ROOM AND CLEAN AIR DEVICE MONITORING

15. (8) Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

16. (9) For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the 4 process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of  $\geq 5.0 \mu\text{m}$  particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

17. (10) It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

18. (11) Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle

losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example those involving live organisms or radiopharmaceuticals.

19. (12) The sample sizes taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean air devices.

20. (13) In Grade A and B zones, the monitoring of the  $\geq 5.0 \mu\text{m}$  particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of  $\geq 5.0 \mu\text{m}$  particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.

21. (14) The particle limits given in the table for the "at rest" state should be achieved after a short "clean up" period of 15-20 minutes (guidance value) in an unmanned state after completion of operations.

22. (15) The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended "clean up period" should be attained.

23. (16) Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

24. (17) Examples of operations to be carried out in the various grades are given in the table N 2 (see also [sections 35 - 42](#) hereto).

Table N 2

Grade	Examples of operations for terminally sterilised products (see <a href="#">sections 35 - 37</a> hereto)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see <a href="#">sections 38 - 42</a> hereto)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

25. (18) Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation.

26. (19) Recommended limits for microbiological monitoring of clean areas during operation are given in table N 3.

Table N 3

Grade	Recommended limits for microbial contamination (a)			
	air sample cfu/m <sup>3</sup>	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes:  
 (a) These are average values.  
 (b) Individual settle plates may be exposed for less than 4 hours.

27. (20) Appropriate limits should be set for the results of particulate and microbiological monitoring: alert and action limits. If these limits are exceeded operating procedures should prescribe corrective action.

#### V. ISOLATOR TECHNOLOGY

28. (21) The utilisation of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary: from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms.

29. (22) The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations. Although it is recognized that laminar air flow may not exist in the working zone of all such devices.

30. (23) The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing it should be at least grade D.

31. (24) Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.

32. (25) Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system.

#### VI. BLOW/FILL/SEAL TECHNOLOGY

33. (26) Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilised should be installed in at least a grade D environment.

34. (27) Because of this special technology particular attention should be paid to, at least the following:  
 equipment design and qualification;

validation and reproducibility of cleaning-in-place and sterilisation-in-place;

background clean room environment in which the equipment is located;

operator training and clothing;

interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

## VII. TERMINALLY STERILISED PRODUCTS

35. (28) Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where the product is at a high or unusual risk of microbial contamination, (for example, because the product actively supports microbial growth or must be held for a long period before sterilisation or is necessarily processed not mainly in closed vessels), then preparation should be carried out in a grade C environment.

36. (29) Filling of products for terminal sterilisation should be carried out in at least a grade C environment.

37. (30) Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, 7 suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilisation.

## VIII. ACEPTIC PREPARATION

38. (31) Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background.

39. (32) Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment. If not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.

40. (33) Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.

41. (34) Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying should be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.

42. (35) Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

## IX. PERSONNEL

43. (36) Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.

44. (37) All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e. g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

45. (38) Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-

organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.

46. (39) High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.

47. (40) Wristwatches, make-up and jewellery should not be worn in clean areas.

48. (41) Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.

49. (42) The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

50. (43) The description of clothing required for each grade is given below:

Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

51. (44) Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.

52. (45) Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

## X. PREMISES

53. (46) In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

54. (47) To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.

55. (48) False ceilings should be sealed to prevent contamination from the space above them.

56. (49) Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.

57. (50) Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back-flow.

58. (51) Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.

59. (52) Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

60. (53) A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10 - 15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.

61. (54) It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.

62. (55) A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

## XI. EQUIPMENT

63. (56) A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).

64. (57) As far as practicable equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out, wherever possible, after complete reassembly.

65. (58) When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.

66. (59) Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.

67. (60) All equipment such as sterilisers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.

## XII. SANITATION

68. (61) The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written program. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.



69. (62) Disinfectants and detergents should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

70. (63) Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

### XIII. PROCESSING

71. (64) Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.

72. (65) Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products. However, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

73. (66) Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.

74. (67) The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations.

75. (68) Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process.

76. (69) The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:

a) when filling fewer than 5 000 units, no contaminated units should be detected;

b) when filling 5 000 to 10 000 units, then:

one (1) contaminated unit should result in an investigation, including consideration of a repeat media fill;

two (2) contaminated units are considered cause for revalidation, following investigation;

c) when filling more than 10 000 units, then:

one (1) contaminated unit should result in an investigation;

two (2) contaminated units are considered cause for revalidation, following investigation.

77. (70) For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

78. (71) Care should be taken that any validation does not compromise the processes.

79. (72) Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.

80. (73) Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of

particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

81. (74) Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

82. (75) Containers and materials liable to generate fibres should be minimised in clean areas.

83. (76) Where appropriate, measures should be taken to minimize the particulate contamination of the end product.

84. (77) Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.

85. (78) The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilisation and use should be minimised and subject to a time-limit appropriate to the storage conditions.

86. (79) The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism-retaining filter should be minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

87. (80) The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate the level of endotoxins should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.

88. (81) Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters.

89. (82) The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

#### XIV. STERILISATION

90. (83) All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the State Pharmacopoeia of the Russian Federation, or when it is used for a product which is not a simple aqueous or oily solution. The method of thermal sterilisation is preferred. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.

91. (84) Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

92. (85) For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.

93. (86) Validated loading patterns should be established for all sterilisation processes.

94. (87) Biological indicators should be considered as an additional method for monitoring the sterilisation. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

95. (88) There should be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.

96. (89) Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.

#### XV. STERILISATION BY HEAT

97. (90) Each heat sterilisation cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.

98. (91) Chemical or biological indicators may also be used, but should not take the place of physical measurements.

99. (92) Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.

100. (93) After the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised unless it can be shown that any leaking container would not be approved for use.

#### XVI. MOIST HEAT

101. (94) Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

102. (95) The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.

103. (96) Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

#### XVII. DRY HEAT

104. (97) The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

## XVIII. STERILISATION BY RADIATION

105. (98) Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.

106. (99) During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.

107. (100) Biological indicators may be used as an additional control.

108. (101) Validation procedures should ensure that the effects of variations in density of the packages are considered.

109. (102) Materials handling procedures should prevent mix-up between irradiated and nonirradiated materials. Radiation sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not.

110. (103) The total radiation dose should be administered within a predetermined time span.

## XIX. STERILISATION WITH ETHYLENE OXIDE

111. (104) This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.

112. (105) Direct contact between gas and microbial cells is essential. Precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

113. (106) Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilisation.

114. (107) Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

115. (108) For each sterilisation cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.

116. (109) After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.

## XX. FILTRATION OF MEDICINAL PRODUCTS WHICH CANNOT BE STERILISED IN THEIR FINAL CONTAINER

117. (110) Filtration alone is not considered sufficient when sterilisation in the final container is possible. Steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-

organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

118. (111) Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

119. (112) Fibre-shedding characteristics of filters should be minimal.

120. (113) The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation. Any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.

121. (114) The same filter should not be used for more than one working day unless such use has been validated.

122. (115) The filter should not affect the product by removal of ingredients from it or by release of substances into it.

## XXI. FINISHING OF STERILE PRODUCTS

123. (116) Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.

124. (117) Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

125. (118) The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.

126. (119) As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.

127. (120) Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped.

128. (121) Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination.

129. (122) Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.

130. (123) Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

131. (124) Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks,

with spectacles if worn. Operators should be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

## XXII. QUALITY CONTROL

132. (125) The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

133. (126) In those cases where parametric release has been authorised ([Annex N 17](#) hereto), special attention should be paid to the validation and the monitoring of the entire manufacturing process.

134. (127) Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e. g.:

a) (a) for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;

b) (b) or products which have been heat sterilised in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

Annex No. 2  
to Good Manufacturing  
Practice

## MANUFACTURE BIOLOGICAL ACTIVE (INCLUDING IMMUNOBIOLOGICAL) ACTIVE SUBSTANCES AND MEDICINAL PRODUCTS

### I. SCOPE

1. The methods employed in the manufacture of biological (including immunobiological) active substances and biological medicinal products (further biological active substances and medicinal products) are a critical factor in shaping the appropriate regulatory control. Biological active substances and medicinal products can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of biological active substances and medicinal products.

2. This annex provides guidance on antibiotics produced at biological stages of production. Guidance for medicinal products derived from fractionated human blood or plasma is covered in [Annex 14](#) hereto, and for non-transgenic plant products in [Annex](#) hereto.

3. This Annex is divided into two main parts:

a) (a) General Guidance ([Part A](#)) contains supplementary guidance on the manufacture of biological active substances and medicinal products, from control over seed lots and cell banks through to finishing activities, and testing.

b) (b) Special Guidance on selected types of products ([Part B](#)) contains further guidance on selected types of biological active substances and medicinal products.

4. There are two aspects to the scope of this Annex:

a) (a) stage of manufacture: for biological active substances to the point immediately prior to their being rendered sterile, the primary guidance source is [Chapter IV](#) hereto. Guidance for the subsequent manufacturing

steps of biological products are covered in [Chapter III](#) hereto;

b) (b) type of product: this annex provides guidance on the full range of medicinal products defined as biological.

5. These two aspects are shown in [Table N 1](#). The level of GMP increases in detail from early to later steps in the manufacture of biological active substances but [GMP](#) principles should always be adhered to.

6. If not otherwise provided by the legislation of the Russian Federation:

a) (a) for tissues and cells which may provide the active substances for some biological medicinal product and other medicinal product;

b) (b) for blood or blood components used as starting materials for medicinal products as concerned the standards of quality and safety for the collection, testing, processing, storage, transportation and distribution of human blood and blood components and the technical requirements for the selection of donors.

c) (c) for the manufacture and control of genetically modified organisms for which appropriate containment and other protective measures shall be established and maintained in facilities where any genetically modified micro-organism are handled in order to establish and maintain the appropriate biological safety level.

Table N 1. The scope of this Annex

1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, immunosera,	Collection of plant, organ, animal material or fluid <1>	Cutting, mixing, and/or initial processing	Isolation and purification	Formulation, filling
2. Virus or bacteria/ fermentation/ cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB <2>, WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotechnology – fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and/or fermentation	Isolation, purification, modification	Formulation, filling
4. Animal sources: transgenic	Recombinant proteins,	Master and working transgenic bank	Collection, cutting, mixing and/or initial processing	Isolation, purification and modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank	Growing, harvesting <3>	Initial extraction, isolation, purification, modification	Formulation, filling
6. Humans sources	Urine derived enzymes, hormones	Collection of fluid	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue/ cells <6>	Manufacture vector <4> and cell purification and processing <5>	Ex-vivo genetic modification of cells, Establish MCB, WCB or primary cell lot	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue/	Establish MCB, WCB or primary cell lot or cell pool	Cell isolation, culture purification, combination with	Formulation, combination, fill

		cells <6>		non-cellular components	
	Tissue engineered products	Donation, procurement and testing of starting tissue/cells <6>	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
Increasing GMP requirements					

See Glossary for explanation of terms and definitions.

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[Sections 87 - 94](#) hereto.

[Sections 54 - 62](#) hereto.

See HMPC guidelines on Good Agricultural and Collection Practice for collection, harvesting and primary processing of herbal starting materials.

Viral vectors are covered by [line 2](#) of this Table.

Technical requirements for tissues and cells used to produce medicinal products are governed by the normative regulations of the Russian Federation.

## II. PRINCIPLE

7. The manufacture of biological medicinal active substances and products involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are manufactured, controlled and administered make some particular precautions necessary.

8. Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and medicinal products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, quality risk management principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.

9. Since materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity to grow. In addition, some products may be limited in their ability to withstand a wide range of purification techniques particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations to minimise such contamination events.

10. Specifications related to products (such as those in Pharmacopoeial monographs, Marketing Authorisation, and Clinical Trial Authorisation) will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. Similarly, manufacturing must be consistent with other specifications set out in the MA or CTA guidance (e.g. number of generations (doublings, passages) between the seed lot or cell bank)

11. For biological materials that cannot be sterilised (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, existing manufacturing practice guidance documents should be consulted on the validation of specific manufacturing methods, e.g. virus removal or



inactivation. The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation systems together with the use of closed systems can significantly reduce the risk of accidental contamination and cross-contamination.

12. Control usually involves biological analytical techniques, which typically have a greater variability than physico-chemical determinations. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

13. Biological medicinal products which incorporate human tissues or cells, for example, certain high-tech medicinal products, must take into account the requirements of the legislation of the Russian Federation as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Collection and testing must be done in accordance with an appropriate quality system for which standards and specifications are defined.

14. Biological active substances and medicinal products must comply with the legal requirements of the Russian Federation in respect to minimising the risk of transmitting animal spongiform encephalopathy agents and latent viruses via Human and Veterinary Medicinal Products.

### III. GENERAL GUIDANCE (PART A)

#### Personnel

15. (1) Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological active substances and products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured to their work, including any specific security measures to protect product, personnel and the environment.

16. (2) The health status of personnel should be taken into consideration for product safety. Where necessary, personnel engaged in production, maintenance, testing and animal care (and inspections) should be vaccinated with appropriate specific vaccines and have regular health checks.

17. (3) Any changes in the health status of personnel, which could adversely affect the quality of the product, should preclude work in the production area and appropriate records kept. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status or chest X-ray. Health monitoring of staff should be commensurate with the risk. Medical advice should be sought for personnel involved with hazardous organisms.

18. (4) Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control (QC), maintenance and cleaning staff) should be controlled on the basis of QRM principles. In general, personnel should not pass from areas where exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, the contamination control measures should be based on QRM principles.

#### Premises and equipment

19. (5) The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the active substance, intermediate or finished product and the production step. The potential level of contamination of the starting materials and the risks to the product should be borne in mind. The environmental monitoring program should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (i.e. host organism, yeast, moulds, anaerobes, etc) where indicated by the QRM process.

20. (6) Manufacturing and storage facilities, processes and environmental classifications should be designed to prevent the extraneous contamination of products. Prevention of contamination is more appropriate than detection and removal, although contamination is likely to become evident during processes such as fermentation and cell culture. Where processes are not closed and there is therefore exposure of the product to the immediate room environment (e.g. during additions of supplements, media, buffers, gasses, during manufacture of high-tech

medicinal products) control measures should be put in place, including engineering and environmental controls on the basis of QRM principles. These QRM principles should take into account the principles and guidance from the appropriate sections of [Annex N 1](#) hereto when selecting environmental classification cascades and associated controls.

21. (7) Dedicated production areas should be used for the handling of live cells capable of persistence in the manufacturing environment. Dedicated production area should be used for the manufacture of pathogenic organisms (i. e. pathogenic groups 1 and 2).

22. (8) Manufacture in a multi-product facility may be acceptable where the following, or equivalent (as appropriate to the product types involved) considerations and measures are part of an effective control strategy to prevent cross-contamination:

a) (a) knowledge of key characteristics of all cells, organisms and any adventitious agents (e. g. pathogenicity, detectability, persistence, susceptibility to inactivation) within the same facility;

b) (b) where production is characterised by multiple small batches from different starting materials factors such as the health status of donors and the risk of total loss of product should be taken into account when considering the acceptance of concurrent working during development of the control strategy;

c) (c) live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and utilizing single use components and engineering measures such as closed systems;

d) (d) control measures to remove the organisms and spores before the subsequent manufacture of other products; Cleaning and decontamination for the organisms and sports should be validated (including heating, ventilation and air conditioning systems);

e) (e) Environmental monitoring specific for the micro-organism being manufactured, where the micro-organisms are capable of persistence in the manufacturing environment and where methods are available, is conducted in adjacent areas during manufacture and after completion of cleaning and decontamination. Attention should also be given to risks arising with use of certain monitoring equipment (e. g. airborne particle monitoring) in areas handling live and/or spore forming organisms.

f) (f) Products, equipment, ancillary equipment (e.g. for calibration and validation) and disposable items are only moved within and removed from such areas in a manner that prevents contamination of other areas, other products and different product stages (e.g. prevent contamination of inactivated or toxoided products with non-inactivated products);

g) (g) campaign-based manufacturing.

23. (9) For finishing (secondary) operation, the need for dedicated facilities will depend on consideration of the above together with additional considerations such as the specific needs of the biological medicinal product and on the characteristics of other products, including any non-biological products, in the same facility. Other control measures for finishing operations may include the need for specific addition sequences, mixing speeds, time and temperature controls, limits on exposure to light and containment and cleaning procedures in the event of spillages.

24. (10) The measures and procedures necessary for containment (i. e. for environment and operator safety) should not conflict with those for product quality.

25. (11) Air handling units should be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas. Besides, there might be need for specific air handling units for certain areas. Consideration, based on QRM principles, should be given to the use of single pass air systems.

26. (12) Positive pressure areas should be used to process sterile products but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of materials with particular risks (e. g. pathogens) they should be surrounded by a positive pressure clean zone of appropriate grade. These pressure cascades should be clearly

defined and continuously monitored with appropriate alarm settings.

27. (13) Equipment used during handling of live organisms and cells, including those for sampling, should be designed to prevent any contamination during processing.

28. (14) Primary containment should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

The use of "clean in place" and "steam in place" ("sterilisation in place") systems should be used where possible. Valves on fermentation vessels should be completely steam sterilisable.

30. (16) Air vent filters should be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles.

31. (17) Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. The legislation of the Russian Federation must be complied with to minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

32. (18) Due to the variability of biological products or manufacturing processes, relevant/critical raw materials (such as culture media and buffers) have to be measured or weighed during the production process. In these cases, small stocks of these raw materials may be kept in the production area for a specified duration based on defined criteria such as for the duration of manufacture of the batch or of the campaign.

#### Animals

33. (19) A wide range of animal species are used in the manufacture of a number of biological medicinal products. These can be divided into 2 broad types of sources:

a) (a) live groups, herds, flocks. Examples include polio vaccine (monkeys), immunosera to snake venoms and tetanus (horses, sheep and goats), allergens (cats), rabies vaccine (rabbits, mice and hamsters), transgenic products (goats, cattle);

b) (b) Animal materials derived post-mortem and from establishments such as abattoirs: examples include abattoir sources for enzymes, anticoagulants and hormones (sheep and pigs).

34. Animals may also be used in quality control either in generic assays, e. g. pyrogenicity, specific potency assays, pertussis vaccine).

35. (20) In addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored by an ongoing health program and recorded. Specialist advice should be obtained in establishing such programs. Instances of ill-health occurring in the source/donor animals should be investigated with respect to their suitability and the suitability of in-contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing), the decisions must be documented. A look-back procedure should be in place which informs the decision-making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced starting or raw materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the program for defined periods.

36. (21) Particular care should be taken to prevent and monitor infections in the source/donor animals. Measures should include the sourcing, facilities, husbandry, biosecurity procedures, testing regimes, control of bedding and feed materials. This is of special relevance to specified pathogen free animals. Housing and health monitoring should be defined for other categories of animals (e. g. healthy flocks or herds).

37. (22) For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals.

38. (23) Note should be taken of the legislation of the Russian Federation on the protection of animals used for scientific purposes, housing, care and quarantine for animals. Housing for animals used in production and control of biological active substances and medicinal products should be separated from production and control areas.

39. (24) For different animal species, key criteria should be defined, monitored, and recorded. These may include age, weight and health status of the animals.

40. (25) Animals, biological agents, and tests carried out should be the subject of an identification system to prevent any risk of confusion and to control all identified hazards.

#### Documentation

41. (26) Starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.

42. (27) Some product types may require specific definition of what materials constitutes a batch, particularly cells used for production of high-tech medicinal products. For autologous and donor-matched situations, the manufactured product should be viewed as a batch.

43. (28) Where human cell or tissue donors are used full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use. Whilst the privacy of individuals and confidentiality of health related information should be maintained. Traceability records must be retained for 30 years after the expiry date of the medicinal product. Particular care should be taken to maintain the traceability of medicinal products for special use cases, such as donor-matched cells. The blood components when they are used as starting or raw materials in the manufacturing process of medicinal products shall comply with existing legal requirements. Where human cells, including hematopoietic stem cells are used to produce highly active substances, traceability is required. The arrangements necessary to achieve the traceability and retention period should be incorporated into technical agreements between the responsible parties.

#### Manufacture

44. (29) Given the variability inherent in many biological active substances and medicinal products, steps to increase process robustness thereby reducing process variability and enhancing reproducibility at the different stages of the product lifecycle. Process design should be reassessed during Product Quality Reviews.

45. (30) Since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state, particular attention should be paid in the control strategy to ensure there are robust steps that prevent or minimise the occurrence of unwanted bioburden and associated metabolites and endotoxins. For medicinal products from cells and tissues where production batches are frequently small the risk of cross-contamination between cell preparations from different donors with various health status should be controlled under defined procedures and requirements.

#### Starting and raw materials

46. (31) The source, origin and suitability of biological starting and raw materials (e. g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available, the risk of using a potentially failed material and its potential impact on other batches should be clearly understood and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. The identification of all starting materials should be in compliance with the requirements appropriate to its stage of manufacture. Biological medicinal products further guidance can be found in [Chapter III](#) and [Annex 8](#) hereto and for biological active substances in [Chapter IV](#) hereto.

47. (32) The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on TSE and latent viruses. Materials that come into direct contact with manufacturing equipment or the product (such as media used in media fill experiments and lubricants that may contact the product) must also be taken into account.

48. (33) Given that the risks from the introduction of contamination and the consequences to the finished product is the same irrespective of the stage of manufacture, establishment of a control strategy to protect the product and the preparation of solutions, buffers and other additions should be based on the principles and guidance contained in the appropriate sections of [Annex N 1](#) hereto. The controls required for the quality of starting materials and on the aseptic manufacturing process, particularly for cell-based products, where final sterilisation is generally not possible and the ability to remove microbial by-products is limited assume greater importance. Where an MA or CTA provides for an allowable type and level of bioburden, for example at active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

49. (34) Where sterilisation of starting and raw materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e. g. irradiation and filtration).

50. (35) Where necessary, other appropriate methods may also be used for inactivation of biological materials (e. g. irradiation and filtration). This should be avoided, but where it is necessary their use should be justified, they should be removed from the manufacturing process at the stage specified in the MA or CTA.

51. (36) Human tissues and cells used as starting or raw materials should comply with the following requirements:

a) (a) their donation, procurement and testing should be in accordance with the normative regulations of the Russian Federation. Supply sites must hold appropriate approvals from the national competent authority(ies) in accordance with the legislation of the Russian Federation. The approvals should be verified as part of starting material supplier management;

b) (b) Where such human cells or tissues are imported from third countries they must meet equivalent standards of quality and safety in accordance with the normative regulations of the Russian Federation;

c) (c) There may be some instances where processing of cells and tissues used as starting materials for biological medicinal products will be conducted at tissue establishments, e. g. to derive early cell lines or banks prior to establishing a master cell bank. In such cases, a responsible person for such processing steps must be delegated in accordance with the legislation of the Russian Federation;

d) (d) Tissue and cells are released by the responsible person in the tissue establishment before shipment to the medicinal product manufacturer, after which normal medicinal product starting material controls apply. The test results of all tissues / cells supplied by the tissue establishment should be available to the manufacturer of the medicinal product. Such information must be used to make appropriate material segregation and storage decisions. In cases where manufacturing must be initiated prior to receiving test results from the tissue establishment. This is possible provided controls are in place to prevent cross contamination with tissue and cells. Tissue and cells that have been released by the responsible person in the tissue establishment may be shipped;

e) (e) the transport of human tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties. The manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions;

f) (f) continuation of traceability requirements started at tissue establishments through to the recipient(s), and vice versa, including materials in contact with the cells or tissues, should be maintained;

g) (g) A technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue establishment, sponsors, MA holder) which defines the tasks of each party, including the responsible person and qualified person).

52. (37) With regard to gene therapy:

a) (a) for products consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, i.e. the master virus seed or the plasmids to transfect the packaging cells and the MCB of the packaging cell line;

b) (b) for products consisting of plasmids, non-viral vectors and genetically modified micro-organisms other than viruses or viral vectors, the starting materials are the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the MCB of the recombinant microbial cells;

c) (c) for genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, i.e. the starting materials to manufacture the vector and the human or animal cell preparations;

d) (d) The principles of [GMP](#) apply from the bank system used to manufacture the vector or plasmid used for gene transfer.

53. (38) Where human or animal cells are used in the manufacturing process as feeder cells, appropriate controls over the sourcing, testing, transport and storage should be in place, including control of compliance with donation, procurement and testing standards in accordance with the legislation of the Russian Federation.

#### Seed lot and cell bank system

54. (39) In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal substances and products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working virus seed lots and/or cell banks. Such system may not be applicable to all types of high-tech medicinal products.

55. (40) The number of generations (doublings, passages) between the seed lot or cell bank, the active biological substance and the finished product should be consistent with specifications in the MA or CTA.

56. (41) As part of product life cycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under circumstances which are demonstrably appropriate. This should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e. g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons. For stages prior to the master seed or cell bank generation, where only the principles of [GMP](#) may be applied, documentation should be available to support traceability. This documentation should include issues related to components used during development with potential impact on product safety (e. g. reagents of biological origin) from initial sourcing and genetic development if applicable.

57. (42) Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures should be followed. This should include adequate characterization and testing for contaminants. Their on-going suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks should be documented. Records should be kept in a manner permitting trend evaluation.

58. (43) Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination, (e. g. stored in the vapor phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and take account the infectious nature of the materials to prevent cross contamination.

59. (44) Cell based medicinal products are often generated from a cell stock obtained from limited number of passages. In contrast with the two tiered system of Master and Working cell banks, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be covered by a validation protocol.

60. (45) Storage containers should be sealed, clearly labeled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be recorded continuously and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

61. (46) It is desirable to split stocks and to store the split stocks at different locations so as to minimize the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs.

62. (47) The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot / cell bank management system, the containers should not be returned to stock.

#### Operating principles

63. (48) Change management should, on a periodic basis, take into account the effects, including cumulative effects of changes (e. g. to the process) on the quality, safety and efficacy of the finished product.

64. (49) Critical operational (process) parameters, or other input parameters which affect product quality, need to be identified, validated, documented and be shown to be maintained within requirements.

65. (50) A control strategy for the entry of articles and materials into production areas should be based on QRM principles. For aseptic processes, heat stable articles and materials entering a clean area or clean/contained area should preferably do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an air lock with interlocked doors where they are subject to effective surface sanitisation procedures. Sterilisation of articles and materials elsewhere is acceptable provided that they are multiple wrappings, as appropriate to the number of stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitisation precautions.

66. (51) The growth promoting properties of culture media should be demonstrated to be suitable for its intended use. If possible, media should be sterilised in situ. In-line sterilising filters for routine addition of gases, media, acids or alkalis, anti-foaming agents etc. to fermenters should be used where possible.

67. (52) Addition of materials or cultures to fermenters and other vessels and sampling should be carried out under carefully controlled conditions to prevent contamination. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.

68. (53) Continuous monitoring of some production processes (e. g. fermentation) may be necessary, such data should form part of the batch record. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.

69. (54) Centrifugation and blending of products can lead to aerosol formation and containment of such activities to minimise cross-contamination is necessary.

70. (55) Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Qualified decontamination measures should be available for each organism or groups of related organisms. Where different strains of single bacteria species or very similar viruses are involved, the decontamination process may be validated with one representative strain, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

71. (56) If obviously contaminated, such as by spills or aerosols, or if a potential hazardous organism is involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means.

72. (57) In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.

73. (58) For products that are inactivated by the addition of a reagent (e. g. micro-organisms in the course of vaccine manufacture) the process should ensure the complete inactivation of live organism. In addition to the thorough mixing of culture and inactivant, consideration should be given to contact of all product-contact surfaces exposed to live culture and, where required, the transfer to a second vessel.

74. (59) A wide variety of equipment is used for chromatography. QRM principles should be used to devise

the control strategy on matrices, the housings and associated equipment when used in campaign manufacture and in multi-product environments. The re-use of the same matrix at different stages of processing is discouraged. Acceptance criteria, operating conditions, regeneration methods, life span and sanitization or sterilisation methods of columns should be defined.

75. (60) Where irradiated equipment and materials are used, [Annex N 12](#) hereto should be consulted for further guidance.

76. (61) There should be a system to assure the integrity and closure of containers after filling where the final products or intermediates represent a special risk and procedures to deal with any leaks or spillages. Filling and packaging operations need to have procedures in place to maintain the product within any specified limits, e. g. time and/or temperature.

77. (62) Activities in handling vials containing live biological agents must be performed in such a way to prevent the contamination of other products or egress of the live agents into the work environment or the external environment. The viability of such organisms and their biological classification should take into consideration as part of the management of such risks.

78. (63) Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific product of the contents on the immediate and outer packaging or on the use of genetic engineering. In the case of autologous products, the unique patient identifier and the statement "for autologous use only" should be indicated on the outer packaging. Where there is no outer packaging, information should be indicated on the immediate packaging.

79. (64) The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified.

80. (65) Where donor (human or animal) health information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.

#### Quality Control

81. (66) In-process controls have a greater importance in ensuring the consistency of the quality of biological active substance and medicinal products than for conventional products. In-process control testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the finished product.

82. (67) Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration should be given to the inclusion of finished product batches made from materials held for their maximum in-process periods in the on-going stability program.

83. (68) Certain types of cells (e. g. autologous cells used for the production of high-tech medicinal products) may be available in limited quantities and, where allowed in the MA, a modified testing and sample retention strategy may be developed and documented.

84. (69) For cellular products, sterility tests should be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and to be able to detection fastidious organisms where appropriate.

85. (70) For biological medicinal products with a short shelf life, which for the purposes of the Annex is taken to mean a period of 14 days or less, and which need batch certification before completion of all end product quality control tests (e. g. sterility tests) a suitable control strategy must be in place. Such controls need to be built on enhanced understanding of product and process performance and take into account the controls and attributes of starting and raw materials. The exact and detailed description of the entire release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical data is essential. A continuous assessment of the effectiveness of the quality assurance system must be in place including records kept in a manner which permit trend evaluation. Where end product tests are not available due to their short shelf life, alternative methods of obtaining equivalent data to permit initial batch certification should be considered (e. g.



rapid microbiological methods). The procedure for batch certification and release may be carried out in two or more stages:

a) (a) assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review in preparation for the initial certification by the qualified person;

b) (b) assessment of the final analytical tests and other information available for final certification by the qualified person.

86. A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence documented.

#### IV. SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES (PART B)

##### Animal Sourced Products (B1)

87. This guidance applies to animal materials which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied. Besides, the requirements of the state monographs of the Russian Federation, including the need for specific tests at defined stages shall be taken into account. Documentation to demonstrate the supply chain traceability and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

88. (1) Monitoring programs should be in place for animal disease that are of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. This should be supplemented by information on health monitoring and control programs at national and local levels, the latter to include the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs. Such an organization is, for example, Office International des Epizooties.

89. (2) Where abattoirs are used to source animal tissues, they should be shown to operate in accordance with the normative regulations of the Russian Federation. Account should be taken of reports from representative authorities who verify compliance with the requirements of food safety and quality specified by the normative regulations of the Russian Federation and in third countries exporting to the Russian Federation.

90. (3) Control measures for starting or raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency.

91. (4) Control measures for starting or raw materials should be in place which prevent interventions which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.

92. (5) Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

93. (6) Cells, tissues and organs intended for the manufacture of xenogeneic cellbased medicinal products should be obtained only from animals that have been bred in captivity (barrier facility) specifically for this purpose. Under no circumstances should cells, tissues and organs from wild animals or from abattoirs be used. Tissues of founder animals similarly should not be used. The health status of the animals should be monitored and

documented.

94. (7) For xenogeneic cell therapy products appropriate normative regulations of the Russian Federation in relation to procurement and testing of animal cells should be followed.

#### ALLERGEN PRODUCTS (B2)

95. Materials may be manufactured by extraction from natural sources or manufactured by recombinant DNA technology.

96. (1) Source materials should be described in sufficient detail to ensure consistency in their supply, e. g. common and scientific name, origin, nature, contaminant limits, method of collection. Those derived from animals should be from healthy sources. Appropriate biosecurity controls should be in place for colonies (e. g. mites, animals) used for the extraction of allergens. Allergen products should be stored under defined conditions to minimise deterioration.

97. (2) The production process steps including pre-treatment, extraction, filtration, dialysis, concentration or freeze-drying steps should be described in detail and validated.

98. (3) The modification processes to manufacture modified allergen extracts (e.g. allergoids, conjugates) should be described. Intermediates in the manufacturing process should be identified and controlled.

99. (4) Allergen extract mixtures should be prepared from individual extracts from single source materials. Each individual extract should be considered as one active substance.

#### Animal Immunoserum Products (B3)

100 (1) Particular care should be exercised on the control of antigens of biological origin to assure their quality, consistency and freedom from adventitious agents. The preparation of materials used to immunise the source animals (e.g. antigens, hapten carriers, adjuvants, stabilising agents), the storage of such material immediately prior to immunisation should be in accordance with documented procedures.

101. (2) The immunisation, test bleed and harvest bleed schedules should conform to those approved in the MA.

102. (3) The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab or  $F(ab')_2$ ) and any further modifications must be in accordance with validated and approved parameters. Where such enzymes are made up of several components, their consistency should be assured.

#### Vaccines (B4)

103. (1) Where eggs are used, the health status of all source flocks used in the production of eggs (whether specified pathogen free or healthy flocks) should be assured.

104. (2) The integrity of containers used to store intermediate products and the hold times must be validated.

105. (3) Vessels containing inactivated products should not be opened or sampled in areas containing live biological agents.

106. (4) The sequence of addition of active ingredients, adjuvants and excipients during the formulation of an intermediate or final product must be in compliance with specifications.

107. (5) Where organisms with a higher biological safety level (e. g. pandemic vaccine strains) are to be used in manufacture or testing, appropriate containment arrangements must be in place. The approval of such arrangements should be obtained from the appropriate national authority(ies). The approval documents should be available for verification.

#### Recombination products (B5)

108. (1) Process condition during cell growth, protein expression and purification must be maintained within validated parameters to assure a consistent product with a defined range of impurities that is within the capability of the process to reduce to acceptable levels. The type of cell used in production may require increased measures to be taken to assure freedom from viruses. For production involving multiple harvest, the period of continuous cultivation should be within specified limits.

109. (2) The purification processes to remove unwanted host cell proteins, nucleic acids, carbohydrates, viruses and other impurities should be within defined validated limits.

#### Monoclonal Antibody Products (B6)

110. (1) Monoclonal antibodies may be manufactured from murine hybridomas, human hybridomas or by recombinant DNA technology. Control measures appropriate to the different source cells (including feeder cells if used) and materials used to establish the hybridoma / cell line should be in place to assure the safety and quality of the product. It should be verified that these are within approved limits. Freedom from viruses should be given particular emphasis. It should be noted that data originating from products generated by the same manufacturing technology platform may be acceptable to demonstrate suitability.

111. (2) Criteria to be monitored at the end of a production cycle and for early termination of production cycles should be verified that these are within approved limits.

112. (3) The manufacturing conditions for the preparation of antibody sub-fragment (e. g. Fab,  $F(ab')_2$ , scF v) and any further modifications (e.g. radio labeling, conjugation, 672 chemical linking) must be in accordance with validated parameters.

#### Transgenic Animal Products (B7)

113. Consistency of starting material from a transgenic source is likely to be more problematic than is normally the case for non-transgenic biotechnology sources. Consequently, there is an increased requirement to demonstrate batch-to-batch consistency of product in all respects.

114. (1) A range of species may be used to produce biological medicinal products, which may be expressed into body fluids (e. g. milk) for collection and purification. Animals should be clearly and uniquely identified and backup arrangements should be put in place in the event of loss of the primary marker.

115. (2) The arrangements for housing and care of the animals should be defined such that they minimise the exposure of the animals to pathogenic and zoonotic agents. Appropriate measures to protect the external environment should be established. A health-monitoring program should be established and results documented. Any incident should be investigated and its impact on the continuation of the animal and on previous batches of product should be determined. Care should be taken to ensure that any therapeutic products used to treat the animals do not contaminate the product.

116. (3) The genealogy of the founder animals through to production animals must be documented. Since a transgenic line will be derived from a single genetic founder animal, materials from different transgenic lines should not be mixed.

117. (4) The conditions under which the product is harvested should be in accordance with MA or CTA conditions. The harvest schedule and conditions under which animals may be removed from production should be performed according to approved procedures and acceptance limits.

#### Transgenic Plant Products (B8)

118. Consistency of starting material from a transgenic source is likely to be more problematic than is normally the case for non-transgenic biotechnology sources. Consequently, there is an increased requirement to demonstrate batch-to-batch consistency of product in all respects.

119. (1) Additional measures, over and above those given in Part A ([sections 15 - 86](#) hereto) may be required to prevent contamination of master and working transgenic banks by extraneous plant materials and relevant adventitious agents. The stability of the gene within defined generation numbers should be monitored.

120. (2) To assure consistency of yield between crops plants should be clearly and uniquely identified. The presence of key plant features, including health status, across the crop should be verified at defined intervals through the cultivation period.

121. (3) Security arrangements for the protection of crops should be defined. Wherever possible, they need to minimise the exposure to contamination by microbiological agents and cross-contamination with non-related plants. Measures should be in place to prevent materials such as pesticides and fertilisers from contaminating the product. A monitoring program should be established and all results documented, any incident should be investigated and its impact on the continuation of the crop in the production program should be determined.

122. (4) Conditions under which plants may be removed from production should be defined. Acceptance limits should be set for materials (e. g. host proteins) that may interfere with the purification process. It should be verified that the results are within approved limits.

123. (5) Environmental conditions (temperature, rain), which may affect the quality attributes and yield of the recombinant protein from time of planting, through cultivation to harvest and interim storage of harvested materials should be documented. When drawing up such criteria normative regulations of the Russian Federation on good agricultural and collection practice for plants should be taken into account.

#### Gene Therapy Products (B9)

124. There are several types of GT medicinal products (GT products containing recombinant nucleic acid sequence(s) or genetically modified organism(s) or virus(es) and GT medicinal products containing genetically modified cells) and all are within the scope of the guidance in [sections 124 - 136](#) hereto. For cell based GT medicinal products, some aspects of guidance in [sections 137 - 144](#) hereto may be applicable.

125. (1) Since the cells used in the manufacture of gene therapy products are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Particular considerations must be applied to the segregation of autologous materials obtained from infected donors. The robustness of the control and test measures for such starting materials, cryoprotectants, culture media, cells and vectors should be based on QRM principles and in line with the MA or CTA. Established cell lines used for viral vector production and their control and test measures should similarly be based on QRM principles. Virus seed lots and cell banking systems should be used where relevant.

126. (2) Factors such as the nature of the genetic material, type of (viral or non-viral) vector and type of cells have a bearing on the range of potential impurities, adventitious agents and cross-contaminations that should be taken into account as part of the development of an overall strategy to minimise risk. This strategy should be used as a basis for the design of the process, the manufacturing and storage facilities and equipment, cleaning and decontamination procedures, packaging, labeling and distribution.

127. (3) The manufacture and testing of GT medicinal products raises specific issues regarding the safety and quality of the final product and safety issues for recipients and staff. A risk based approach for operator, environment and patient safety and the implementation of controls based on the biological hazard class should be applied. Legislated safety measures applicable in the Russian Federation should be applied.

128. (4) Personnel (including QC and maintenance staff) and material flows, including those for storage and testing (e.g. starting materials, in-process and final product samples and environmental monitoring samples), should be controlled on the basis of QRM principles. Where possible, unidirectional flows are used. This should take into account movement between areas containing different genetically modified organisms and areas containing non-genetically-modified organisms.

129. (5) Any special cleaning and decontamination methods required for the range of organisms being handled should be considered in the design of facilities and equipment. Where possible, the environmental monitoring program should be supplemented by the inclusion of methods to detect the presence of the specific

organisms being cultivated.

130. (6) Where replication limited vectors are used, measures should be in place to prevent the introduction of wild-type viruses, which may lead to the formation of replication competent recombinant vectors.

131. (7) An emergency plan for dealing with accidental release of viable organisms should be in place. This should address methods and procedures for containment, protection of operators, cleaning, decontamination and safe return to use. An assessment of impact on the immediate products and any others in the affected area should also be made.

132. (8) Facilities for the manufacture of viral vectors should be separated from other areas by specific measures. The arrangements for separation should be demonstrated to be effective. Closed systems should be used wherever possible. Simple collection additions and transfers should prevent the release of viral material.

133. (9) Concurrent manufacture of different viral gene therapy vectors in the same area is not acceptable. Concurrent production of non-viral vectors in the same area should be controlled on the basis of QRM principles. Changeover procedures between campaigns should be demonstrated to be effective.

134. (10) A description of the production of vectors and genetically modified cells should be available in sufficient detail to ensure the traceability of the products from the starting material (plasmids, gene of interest and regulatory sequences, cell banks, and viral or non viral vector stock) to the finished product.

135. (11) Shipment of products containing or consisting of GMO should conform to appropriate legislation.

136. (12) The following considerations apply to the ex-vivo gene transfer to recipient cells:

a) (a) these should take place in facilities dedicated to such activities where appropriate containment arrangements exist;

b) (b) measures (including considerations outlined in [section 24](#) in this Annex) to minimise the potential for cross-contamination and mix-up between cells from different patients are required. This should include the use of validated cleaning procedures. The concurrent use of different viral vectors should be subject to controls based on QRM principles. Some viral vectors (e.g. Retro- or Lenti-viruses) cannot be used in the manufacturing process of genetically modified cells until they have been shown to be devoid of replication-competent contaminating vector;

c) (c) traceability requirements must be maintained. There should be a clear definition of a batch, from cell source to final product container(s);

d) (d) for products that utilise non-biological means to deliver the gene, their physico-chemical properties should be documented and tested.

#### Somatic and Xenogeneic Cell Therapy Products and Tissue Engineered Products (B10)

For genetically modified cell based products that are not classified as GT products, [sections 124 - 136](#) hereto may be applicable.

138. (1) Where they are available, authorised sources (i.e. authorised medicinal products or CE marked medical devices) of additional substances (such as cellular products, bio-molecules, bio-materials, scaffolds, matrices) should be used in the manufacture of these products.

139. (2) Where devices, including custom-made devices, are incorporated as part of the products:

a) (a) there should be written agreement between the manufacturer of the medicinal product and the manufacturer of the medical device, which should provide enough information on the medical device to avoid alteration of its properties during manufacturing of the ATMP. This should include the requirement to control changes proposed for the medical device;

b) (b) The technical agreement should also require the exchange of information on deviations in the

manufacture of the medical device.

140. (3) Since somatic cells are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors. The robustness of the control and test measures put in place for these source materials should be ensured.

141. (4) Manufacturing steps should be conducted aseptically where sterilisation of the finished product cannot be achieved using standard methods such as filtration.

142. (5) Careful attention should be paid to specific requirements at any cryopreservation stages, e.g. the rate of temperature change during freezing or thawing. The type of storage chamber, placement and retrieval process should minimise the risk of cross-contamination, maintain the quality of the products and facilitate their accurate retrieval. Documented procedures should be in place for the secure handling and storage of products with positive serological markers.

143. (6) Sterility tests should be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination. The detection of fastidious organism requiring special cultivation conditions should be followed.

144. (7) Where relevant, a stability-monitoring program should be in place together with reference and retain samples in sufficient quantity to permit further examination.

## V. TERMS AND DEFINITIONS

145. For the purposes of this Annex, the following basic concepts are also used, in addition to the terms and definitions provided for in [Chapter II](#) of this GMP:

adjuvant - a chemical or biological substance that enhances the immune response to the antigen;

allergens - substances of antigenic or hapten nature, capable of inducing allergy or specific susceptibility;

allergoids - chemically altered allergens with reduced reactivity of immunoglobulin E (IgE);

antigens - substances (such as toxins, foreign proteins, bacteria, tissue cells) that can induce specific immune responses;

monoclonal antibodies (mAbs) are homogeneous antibody population which binds to a single epitope (antigenic determinant), obtained from a single clone of lymphocytes or by recombinant DNA technology;

polyclonal antibodies derived from a range lymphocyte clones and (or) produced in human or animal organisms in response to antigen administration;

antibody - proteins produced by B-lymphocytes that specifically bind to certain antigens. Antibodies may be divided into two main types - monoclonal and polyclonal antibodies – based on key differences in their methods of production;

cell bank - a set of corresponding containers stored under certain conditions, the contents of which have a uniform composition. The contents of each container is multiple single pool of cells;

biological pharmaceutical substance - a pharmaceutical substance produced using a biological source or extracted from a biological source that must be characterized by means of physical, chemical and biological tests. Its quality is determined by these tests in conjunction with the control of its production processes;

biological medicinal product - a medicinal product whose pharmaceutical substance is a biological pharmaceutical substance;

bioburden - the level and type (for example, objectionable or not) of microorganisms that may be present in the starting materials; starting materials for the production of a pharmaceutical substance, intermediates or in a

pharmaceutical substance. Regarded as a contamination when its level exceeds the established limit values, or microorganisms identified as objectionable are detected;

vector is a transmission agent that delivers genetic information from one cell or organism to another one, for example, plasmids, liposomes, viruses;

viral vector is a vector produced by modifying a virus using molecular biology techniques to retain some, but not all, of the maternal genes of the virus. When removing genes responsible for the virus's ability to replicate, the created vector is incapable of replication;

outside the living organism - a process in which the procedures are performed on tissues or cells outside the living organism with the subsequent return of tissues or cells to the living organism;

inside the living organism - procedures carried out inside living organisms;

excipients - substances of inorganic or organic origin used in the process of production, manufacture of medicinal products to give them the necessary physico-chemical properties <\*>, except for pharmaceutical substances and packaging material;

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<\*> Paragraph 3 of Article 4 of the Federal Law of April 12, 2010. Federal Law No. 61-FZ of 12.04.2010 "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Art. No.1815)

hapten - a molecule not immunogenic by itself but that, when coupled to a macromolecular carrier, can elicit antibodies directed against itself.

gene is a DNA sequence encoding one or more proteins;

genetically modified organism (GMO) - any organism, with the exception of the human body, whose genetic makeup has been altered in such a way that it is impossible to achieve such a change as a result of natural crossing and (or) natural recombination;

hybridoma is an immortalized ("immortal") cell line that secretes desired (monoclonal) antibodies and which is typically derived by artificially fusing B-lymphocytes with tumor cells;

master cell bank is an aliquot of a single pool of cells that has been prepared from a selected cell clone under defined conditions, dispensed into a variety of containers and stored under defined conditions;

master virus seed is an aliquot of a single virus pool that was obtained from a particular virus clone under certain conditions, distributed into many containers and stored under certain conditions;

master transgenic bank is an aliquot of a single pool of cells of transgenic plants or animals that was obtained from a particular cell clone under certain conditions, distributed into a variety of containers and stored under certain conditions;

closed system - a system in which a pharmaceutical substance or a medicinal product does not have direct contact with the work environment;

area - a certain set of premises within a single building in which one or more medicinal drugs are manufactured and which have a separate air handling system;

zoonosis - infectious and invasive diseases of animals that can be transmitted to humans;

contained use - any activity in which genetically modified organisms are produced, cultivated, stored, transported, destroyed, desposed or used in any way; and that is carried out under special containment measures to limit the spread of these organisms and ensure public safety and environmental protection;

starting materials - all materials from which a medicinal product or a pharmaceutical substance is produced

or extracted, with the exception of packaging materials. For biological medicinal products, starting materials are any substances of biological origin, such as microorganisms, organs and tissues of plant or animal origin, cells or liquids (including blood and plasma) of human or animal origin, as well as biotechnological cellular substrates (recombinant and natural ones) including primary cells;

cell stock - primary cells expanded to a given number of cells, to be aliquoted and used as a starting material for production of a limited number of lots of a cell-based medicinal product;

responsible person - a specially appointed person in the organization for production of biological (including immunobiological) pharmaceutical substances and medicinal products, which is responsible for:

ensuring that biological material (including human cells and / or tissues) is obtained, tested, used in production process of a medicinal product, including quality control of the finished product, and was stored and released in accordance with the legislation of the Russian Federation;

providing the authorized federal executive bodies with the necessary information regarding regulations, permits, accreditation or licensing;

performance in the organization for the production of biological (including immunobiological) pharmaceutical substances and medicinal products of all requirements of the legislation of the Russian Federation.

The responsible person must meet the following qualification conditions:

have a higher medical, pharmaceutical or biological education;

have a work experience of at least two years in one or more organizations of the relevant profile.

The above responsibilities of the responsible person can be transferred to other persons who have the appropriate qualifications and work experience to fulfill these responsibilities.

Organizations for the production of biological (including immunobiological) pharmaceutical substances and medicinal products shall advise the authorized federal executive body on surname, first name and patronymic (if any) of the responsible person, as well as persons to whom the responsibilities of the responsible person are transferred, together with information on specific responsibilities that are assigned to them.

If the responsible person or persons to whom their responsibilities have been transferred, are replaced on a permanent basis or as interim by another person, the organization for the production of biological (including immunobiological) pharmaceutical substances and medicinal products shall immediately notify the authorized federal executive body of surname, first name and patronymic (if any) a new responsible person and the date of his appointment;

gene transfer - the process of gene delivery into cells, including the expression system contained in the delivery system, which is called the vector. The vector can be of either viral or non-viral origin. After gene transfer, genetically modified cells can also be called "transformed cells";

feeder cells - cells used in co-culture to maintain pluripotency (ability to differentiate into a variety of specialized cell types) of stem cells. For human embryonic stem cell culture, typical feeder layers include mouse embryonic fibroblasts (EFM) or human embryonic fibroblasts (ESP), that have been treated to prevent them from dividing;

plasmid - a part of the DNA that normally exists in the bacterial cell as a ring structure separated from the cell chromosomes. The plasmid can be modified by molecular biology methods, isolated from a bacterial cell and used to transfer and integrate its DNA into the genome of another cell;

scaffold - a support tool, delivery vehicle or matrix that provides a structure or facilitates the migration, binding or transport of cells and / or biologically active molecules;

multi-product facility - a premise for sequential manufacture or campaign-(based) manufacture of various groups of biological pharmaceutical substances and medicinal products. The different groups of substances or



medicinal products may be run on the same equipment or not.

deliberate release - a deliberate release into the environment of genetically modified organisms for which no special containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment;

campaign-(based) production - the manufacture of an uninterrupted sequence of batches of the same product or intermediate in a given time period, followed by strict adherence to accepted control measures before switching to another product or different serotype. The different products are not run at the same time but may be run on the same equipment;

look-back - a documented procedure that monitors biological pharmaceutical substances or medicinal products of inappropriate quality due to the use of rejected animal or human materials due to the presence of contaminating agent (s) in these materials or in the detection of negative factors in animals or humans, which are the source of these materials;

working cell bank (WCB) - a homogeneous pool of microorganisms or cells derived from master cell bank and uniformly dispensed into a specific number of containers. The working cell bank is stored under conditions that ensure its stability and use in production;

working virus seed (stock) (WVS) is a homogeneous pool of viruses derived from master virus seed and uniformly dispensed into a specific number of containers. The working virus seed is stored under conditions that ensure its stability and use in production;

working transgenic bank - a homogeneous pool of cells of transgenic plants or animals derived from master transgenic bank and uniformly dispensed into a specific number of containers. The working transgenic bank is stored under conditions that ensure its stability and use in production;

Specific-pathogen-free (SPF) - animal materials (for example, chickens, embryos or cell cultures) used for the production or quality control of biological medicinal products derived from groups of animals (for example, flocks of herds) free of particular pathogens. Such flocks or herds are defined as groups of animals sharing a common environment and having their own caretakers who have no contact with non-SPF animals;

somatic cells - all cells of a human or animal organism, other than reproductive cells. These cells can be autologous (from the same patient), allogeneic (from another person) or xenogeneic (from animals) somatic living cells, that have been manipulated or modified under conditions outside the living organism with subsequent introduction into the human body to achieve therapeutic, diagnostic or prophylactic action;

transgenic - an organism containing a foreign gene in its normal genetic structure for the expression of biological pharmaceutical materials;

biosafety level - the containment conditions required for safe work with microorganisms of different levels of pathogenicity, starting from the 4th pathogenicity group (the lowest risk, which is unlikely to lead to human disease) and up to the 1st pathogenicity group (the highest risk causing severe easily spreading diseases);

pure (axenic) culture - a culture that contains the same microorganisms and is not contaminated by any other organisms.

Annex No. 3  
to Good Manufacturing  
Practice

## PRODUCTION OF RADIOPHARMACEUTICALS

## I. PRINCIPLE

1. The manufacture of radiopharmaceuticals(RPh) shall be undertaken in accordance with the principles principles set forth in [Chapters III - IV](#) of the Practice. This Annex addresses some of the practices, which may be specific for radiopharmaceuticals.

2. In applying [the Practice](#) the following should be considered:

a) this Annex does not apply to the manufacture of radiopharmaceuticals in pharmacy institutions and veterinary pharmacy institutions;

б) This Annex is also applicable to radiopharmaceuticals used in clinical trials;

в) Transport of radiopharmaceuticals is regulated by radiation protection requirements of the International Atomic Energy Association (IAEA) and the requirements of regulatory legal acts of the Russian Federation;

г) It is recognised that there are acceptable methods, other than those described in this Annex, which are capable of achieving the principles of Quality Assurance. Such methods should be validated and provide a quality level not lower than the quality level in accordance with the requirements established by this Annex.

## II. INTRODUCTION

3. (1) The production and handling of radiopharmaceuticals is potentially hazardous. The level of risks depends, in particular, upon the type of ionizing radiation, energy of radiation, and half-lives of radionuclides. Particular attention should be paid to the prevention of cross-contamination, to retention of radioactive material residues and to waste disposal.

4. (2) Due to short shelf life of their radionuclides, some radiopharmaceuticals containing them may be released before completion of all quality control tests. In this case, the exact and detailed description of the whole release procedure including the responsibilities of the involved personnel and the continuous assessment of the effectiveness of the quality assurance system is essential.

5. (3) This guideline is applicable to manufacturing procedures employed by industrial manufacturers, Nuclear Centres/Institutes and PET Centres for the production and quality control of the following types of products:

radiopharmaceuticals;

Positron Emitting (PET) Radiopharmaceuticals;

radioactive precursors for production of radiopharmaceuticals;

radionuclide generators.

Type of manufacture	Non GMP y <*>	It is necessary to comply with the requirements of <a href="#">Chapters III - IV</a> of this Practice (as the production stage approaches the finished product, the requirements are strengthened), including the relevant Annexes			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive precursors	Reactor/Cyclotron Production <1>	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic production or final sterilisation
Radionuclide generators	Reactor/Cyclotron Production <2>	Processing (assembly of a column, a generator, charging of a generator)			

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<\*> Target and transfer system from cyclotron to synthesis rig may be considered as the first step of active substance manufacture.

<1> Products obtained as a result of radiochemical separation of a radionuclide from an irradiated radioactive target.

<2> Products obtained as a result of radiochemical separation of a parent radionuclide from the irradiated radioactive target.

6. (4) The manufacturer of the final radiopharmaceutical should describe and justify the steps for manufacture of the active substance and the final medicinal product and which requirements of the Practice ([Chapter III](#) or [Chapter IV](#) of the GMP applies for the specific process/manufacturing operations or steps.

7. (5) Preparation of radiopharmaceuticals involves adherence to requirements of radiation safety [standards](#).

8. (6) Radiopharmaceuticals to be administered parenterally should comply with sterility requirements for parenterals and, where relevant, aseptic working conditions for the manufacture of sterile medicinal products, which are covered in [Annex No. 1](#) to GMP.

9. (7) Specifications and quality control testing procedures for radiopharmaceuticals are specified in the State Pharmacopoeia of the Russian Federation or in in the marketing authorisation.

#### Clinical trials

10. (8) Radiopharmaceuticals intended for use in clinical trials as investigational medicinal products should in addition be produced in accordance with the principles of [Annex No. 13](#) to the Practice.

### III. QUALITY ASSURANCE

11. (9) Quality assurance is of even greater importance in the manufacture of radiopharmaceuticals because of their particular characteristics, low volumes and in some circumstances the need to administer the product before quality control operations are complete.

12. (10) As with all pharmaceuticals, the products must be well protected against contamination and cross-contamination. In this case, the environment and the operators must also be protected against ionizing radiation.

13. (11) Proper registration of premises and processes monitoring data is of the utmost importance. It is important that the data generated by such monitoring are rigorously recorded and evaluated as part of the release process.

14. (12) The principles of qualification and validation should be applied to the manufacturing of radiopharmaceuticalsto the extent required. A risk management approach should be used to determine the extent of qualification/validation, focusing on a combination of this [Practice](#) and Radiation Protection.

### IV. PERSONNEL

15. (13) All operations must be performed under the responsibility of personnel with additional competence in radiation protection. Personnel involved in the production, quality control and release of radiopharmaceuticals should be appropriately trained in radiopharmaceutical specific aspects of the quality management system. The qualified person (QP) should have the overall responsibility for release of the radiopharmaceuticals.

16. (14) All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured should receive appropriate additional training specific to these types of procedures and products.

17. (15) Where production facilities are shared with research institutions, the research personnel must be adequately trained in [Practice](#). Quality assurance activities consist of reviewing and approving the research activities to ensure that they do not pose any hazard to the manufacturing of radiopharmaceuticals.

## V. PREMISES AND EQUIPMENT

### General

18. (16) Radioactive products should be manufactured in controlled (environmental and radioactive) areas. All manufacturing steps should take place in self-contained facilities and on special equipment dedicated to radiopharmaceuticals.

19. (17) Measures should be established and implemented to prevent cross-contamination from personnel, starting materials, materials, radionuclides. Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, precautions should be taken to minimize the risk of contamination. The risk assessment should demonstrate that the environmental cleanliness level proposed is suitable for the type of product being manufactured.

20. (18) Access to the manufacturing areas should be via gowning rooms (decontamination stations) and should be restricted to authorised personnel.

21. (19) Workstations and their environment should be monitored with respect to radioactivity, particulate and microbiological quality. The procedure for monitoring is established during performance qualification (PQ).

22. (20) Preventive maintenance, calibration and qualification programmes should be operated to ensure that all facilities and equipment used in the manufacture of radiopharmaceutical are suitable and qualified. These activities should be carried out by competent personnel, and records and logs should be maintained.

23. (21) Precautions should be taken to avoid radioactive contamination within the facility. Appropriate controls should be in place in the prescribed manner to detect any radioactive contamination either directly through the use of radiation detectors (dosimeters) or indirectly through a swabbing routine.

24. (22) Equipment should be constructed so that surfaces that come into contact with the product are not reactive, additive or absorptive so as to alter the quality of the radiopharmaceutical.

25. (23) Recirculation of air extracted from area where radiopharmaceuticals are handled should be avoided unless justified. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases. Appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination.

26. (24) In order to contain radioactive particles, it may be necessary for the air pressure to be lower where products are exposed, compared with the surrounding areas. However, it is still necessary to protect the product from contamination of the production environment. This may be achieved by, for example, using barrier technology and air locks, operating on principle of pressure cascade.

### Manufacture of sterile products

27. (25) Sterile radiopharmaceuticals are divided into two groups: medicinal products which are manufactured aseptically, and those, which are terminally sterilised. The facility should maintain the appropriate level of environmental cleanliness for the type of operation being performed. For manufacture of sterile products the working area where products or containers (primary packaging) may be exposed to the environment, the cleanliness requirements should comply with the requirements described in [Annex No. 1](#) to this Practice.

28. (26) For manufacture of radiopharmaceuticals a risk assessment may be applied to determine the appropriate pressure differences, air flow direction and air quality.

29. (27)) In case of use of closed and automated systems (chemical synthesis, purification, on-line sterile filtration) a grade C environment (usually "Hot-cell") will be suitable. Hot-cells should meet a high degree of air

cleanliness, with filtered feed air, when closed. Aseptic activities must be carried out in a grade A area.

30. (28) Prior to the start of manufacturing, assembly of sterilised equipment and consumables (tubing, sterilising filters and sterile closed and sealed vials to a sealed fluid path) must be performed under aseptic conditions

## VI. DOCUMENTATION

31. (29) All documents related to the manufacture of radiopharmaceuticals should be prepared, reviewed, approved and distributed according to written procedures.

32. (30) Specifications should be established and documented for raw materials, labelling and packaging materials, critical intermediates and the finished radiopharmaceutical. Specifications should also be in place for any other critical items used in the manufacturing process, such as process aids, gaskets, sterile filtering kits, that could critically impact on quality.

33. (31) Acceptance criteria should be established for the radiopharmaceuticals, including including criteria for release and shelf life specifications (for example, radiochemical purity, radioactive concentration, radionuclide purity and specific activity).

34. (32) Records of major equipment use, cleaning, decontamination or sterilisation and maintenance should show date and time of the operation completed as well as signature for the persons involved in these activities. Product name and batch number are also indicated, where appropriate.

35. (33) Records shall be retained for at least three years, unless another timeframe is specified in the regulatory legal acts of the Russian Federation.

## VII. MANUFACTURE

36. (34) Production of different radiopharmaceuticals in the same working area (i.e. hot-cell, LAF unit), at the same time should be avoided in order to minimise the risk of radioactive cross-contamination or mix-up.

37. (35) Particular attention should be paid to validation, including validation of computerised systems which should be carried out in accordance with [Annex No. 11](#) to the Practice. New manufacturing processes must undergo prospective validation.

38. (36) The critical parameters should normally be identified before or during validation. The ranges of permissible limit values of the parameter changes, necessary for reproducible operation should be defined.

39. (37) Integrity testing of the membrane filter should be performed for aseptically filled products, taking into account the need for radiation protection and maintenance of filter sterility.

40. (38) Due to radiation exposure it is accepted that most of the labelling of the direct container, is done prior to manufacturing. The sterile empty closed vials may be labeled with partial information prior to the filling operation providing that this procedure does not compromise sterility and or prevent visual control of the filled vials.

## VIII. QUALITY CONTROL

41. (39) Some radiopharmaceuticals may have to be distributed and used on the basis of an assessment of batch documentation and before all chemical and microbiology tests have been completed.

42. Radiopharmaceutical product release may be carried out in two or more stages, before and after full analytical testing:

a) (a) Assessment by a designated person of batch processing records, which should cover production conditions and analytical testing performed thus far, before allowing transportation of the radiopharmaceutical under quarantine status to the clinical department.

6) (b) Assessment of the final analytical data, ensuring all deviations from normal procedures are documented, justified and appropriately released prior to documented certification by the Qualified Person. Where certain test results are not available before use of the product, the Qualified Person should conditionally certify the product before it is used and should finally certify the product after all the test results are obtained.

43. (40) Most radiopharmaceuticals are intended for use within a short time and the period of validity with regard to the radioactive shelf-life, must be clearly stated.

44. (41) Radiopharmaceuticals containing radionuclides with long half-lives should be tested to show, that they meet all relevant acceptance criteria before release and certification by the QP.

45. (42) Before testing is performed samples can be stored to allow sufficient radioactivity reduction. All tests including the sterility test should be performed as soon as possible.

46. (43) A written procedure detailing the assessment of production and analytical data, which should be considered before the batch is dispatched, should be established.

47. (44) Products that fail to meet acceptance criteria should be rejected. If the material is reprocessed, preestablished procedures should be followed. The finished product should meet acceptance criteria before release. It is not allowed to recycle the returned products, which should be disposed as radioactive waste.

48. (45) A procedure should also describe the measures to be taken by the Qualified Person if unsatisfactory test results (Out-of-Specification) are obtained after dispatch and before expiry. Such events should be investigated, to include the relevant corrective and preventative actions taken to prevent future events. This process should be documented.

49. (46) Information should be given to the clinical responsible persons, if necessary. To facilitate this, traceability should be provided for radiopharmaceuticals.

50. (47) A system to verify the quality of starting materials should be in place. Supplier selection and approval should include an evaluation that provides adequate assurance that the material consistently meets specifications. Starting materials, packaging materials and critical process aids should be purchased only from approved suppliers.

## IX. REFERENCE AND RETAINED SAMPLES

51. (48) For radiopharmaceuticals sufficient samples of each batch of bulk formulated product shall be retained for at least six months after expiry of the finished medicinal product unless otherwise justified through risk management.

52. (49) Samples of starting materials, other than solvents gases or water used in the manufacturing process shall be retained for at least two years after the release of the product. This period may be shortened if the period of stability of the material as indicated in the relevant specification is shorter.

53. (50) Other conditions may be defined by agreement with the competent authority, for the sampling and retaining of starting materials and products manufactured individually or in small quantities or when their storage could raise special problems.

## X. DISTRIBUTION

Distribution of the finished product under controlled conditions, before all appropriate test results are available, is acceptable for radiopharmaceuticals, providing the product is not administered by the receiving institute until satisfactory test results has been received and assessed by a designated person.

## XI. TERMS AND DEFINITIONS

55. For the purposes of this Annex, the following basic concepts are also used, in addition to the terms and definitions provided for in of this Regulation: [Chapter II](#) of the Practice:

hot cell - shielded or not shielded workstation for manufacture and handling of radioactive materials;

preparation - handling and radiolabelling of kits with radionuclide eluted from generators or radioactive precursors within a hospital. Kits, generators and precursors should have a marketing authorisation or a national licence.

radioactive precursor - a radioactive substance intended to introduce a radionuclide label into another substance before its use;

radiopharmaceuticals - medicinal products that contain one or more radionuclides (radioactive isotopes) in the form ready for use <\*>.

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<\*> Paragraph 10 of Article 4 of the Federal Law of April 12, 2010. Federal Law No. 61-FZ of 12.04.2010 "On Circulation of Medicines" (Collected Acts of the Russian Federation, 2010, No. 16, Art. No.1815)

Annex No. 4  
to Good Manufacturing  
Practice

SPECIFICS  
OF MANUFACTURE OF MEDICINAL PRODUCTS FOR VETERINARY  
USE OTHER THAN IMMUNOLOGICAL  
VETERINARY MEDICINAL PRODUCTS

1. This Annex applied to all medicinal products for veterinary use, other than immunological veterinary medicinal products, which are the subject of [Annex No. 5](#) to the Practice.

I. MANUFACTURE OF THE MEDICINAL PRODUCTS  
AGAINST ECTOPARASITES

2. (5) In derogation from [paragraph 52](#) of this Practice, ectoparasiticides (medicinal products against ectoparasites) for external application to animals, which are veterinary medicinal products, and subject to marketing authorisation, may be produced and filled on a campaign basis in pesticide specific areas. However, other categories of medicinal products for veterinary use should not be produced in such areas.

3. (6) Adequate validated cleaning procedures should be employed to prevent prevent cross-contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the requirements of this [Practice](#).

II. MANUFACTURE OF MEDICINAL PRODUCTS FOR VETERINARY  
USE, CONTAINING PENICILLINS

4. (7) The use of penicillins in veterinary medicine does not represent the same risk of hypersensitivity in animals, as in humans. Although incidents of hypersensitivity have been recorded in horses and dogs, there are other materials which are toxic to certain species, e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross-contamination and and any risk to operator safety in accordance with the requirements of this [Practice](#). When using common premises, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.



### III. RETENTION OF SAMPLES

ConsultantPlus: note.

See also Decree of RF Ministry of Agriculture of 15.04.2015 No. 145 regarding the order of storage of medicinal products for veterinary use.

5. (8) It is recognised that because of the large volume of certain veterinary medicinal products in their final packaging, in particular premixes, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, the manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the requirements of this [Practice](#).

6 (9) In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

### IV. STERILE MEDICINAL PRODUCTS FOR VETERINARY USE

7. (10) In cases provided for by the regulatory legal acts of the Russian Federation, terminally sterilised veterinary medicinal products may be manufactured in a clean area of a lower grade than the grade required in the veterinary medicinal products subject to [Annex No. 1](#) to the Practice, but but at least in a grade D environment.

Annex No. 5  
to Good Manufacturing  
Practice

### SPECIFICS OF MANUFACTURE OF IMMUNOBIOLOGICALS FOR VETERINARY USE

#### I. PRINCIPLE

1. Manufacture of immunological veterinary medicinal products has special characteristics which should be taken into consideration when implementing and evaluating the pharmaceutical quality system.

2. Due to the large number of animal species and related pathogenic microorganisms, the range of products manufactured is very wide and the volume of manufacture is often low. Hence, work on a campaign basis is common. Moreover, because of the very nature of such manufacture (cultivation stages, lack of terminal sterilisation, etc.), the products must be particularly well-protected against contamination and cross-contamination. The environment also must be protected especially, when the manufacture involves the use of pathogenic or exotic biological agents. The personnel must be particularly well protected when the manufacture involves the use of microorganisms, pathogenic to man.

3. These factors, together with the inherent variability of immunobiologicals and the relative inefficiency in particular of final product quality control tests in providing adequate information about products, means that, the role of the pharmaceutical quality assurance system is of the utmost importance.

#### II. PERSONNEL

(1) All employees (including those concerned with cleaning and maintenance of premises and equipment) working in the areas where immunological products are manufactured should be given training in and information on personal hygiene and microbiology. They should receive additional training specific to the products with which

they work.

(2) Responsible personnel should be formally trained, in accordance with their roles, in some or all of the following fields: bacteriology, biology, biometry, chemistry, immunology, medicine, parasitology, pharmacy, pharmacology, virology and veterinary medicine, and should also have an adequate on knowledge of environmental protection measures.

(3) The personnel should be protected against possible contamination with microorganisms used in manufacture. In the case of biological agents known to cause disease in humans, adequate measures should be taken to prevent infection of personnel working with these pathogens or experimental animals.

7. Where relevant, staff should be vaccinated. The personnel should also be subject to health examination.

8. (4) Adequate measures should be taken against the escape of microorganisms outside the production area by personnel acting as a carrier. Depending on the type of biological agent, such measures may include complete gowning and compulsory showering before leaving the production area.

9. (5) For immunobiological products, the risk of contamination and cross-contamination by personnel is particularly important. Prevention of contamination by personnel should be achieved by a set of measures and procedures, including use of protective clothing at various stages of the production process.

10. Prevention of cross-contamination by personnel involved in production should be achieved by a set of measures and procedures to ensure that they do not pass from one area to another unless they have taken appropriate measures to eliminate the risk of contamination. These rules should be stated in the instructions. During working hours, personnel should not pass from areas with exposure to contamination from live microorganisms is likely or from animal facilities to areas where other products or microorganisms are handled. If such passage is unavoidable, well-established decontamination measures, such as change of clothing and shoes, and, where necessary, showering, should be followed by the personnel involved in such production.

11. For the purpose of this Annex, personnel entering a contained area where organisms had not been handled in open circuit operations in the previous twelve hours to check on cultures in sealed, surface decontaminated flasks would not be regarded as being at risk of contamination, unless the organism involved was an exotic.

### III. PREMISES

(6) Premises should be designed in such a way as to control both the risk to the product and to the environment. This can be achieved by using contained, clean, clean /contained or controlled areas.

(7) Operations with live microorganisms should be carried out in contained areas. The level of containment should depend on the pathogenicity of the microorganism and whether it has been classified as exotic.

14. (8) Operations with inactivated microorganisms should be handled in clean areas. Clear areas should also be used when handling non-infected cells isolated from multicellular organisms, and in some cases, filtration-sterilised media.

(9) Open circuit operations involving products or components not subsequently sterilised should be carried out within a laminar air flow work station (grade A) in a grade B area.

16. (10) Other operations where live biological agents are handled (quality control, research and diagnostic services, etc.) should be appropriately contained and separated if production operations are carried out in the same building. The level of containment depends on pathogenicity of the specific type of microorganism and whether it has been classified as exotic. When performing diagnostic operations, there is a risk of ingress of highly pathogenic microorganisms. The level of containment shall should be adequate to cope with all of the above mentioned risks. Containment may also be required in cases where quality control and other operations are carried out in buildings in close proximity to those used for production.

17. (11) Containment premises should be easily disinfected and should have the following characteristics:

a) (a) absence of direct venting to the outside;

b) (b) ventilation with air at negative pressure (rarefaction). Air should be extracted through filters- high-efficiency particulate absorbers (hereinafter referred to as HEPA filters), and not be recirculated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the recirculated air through the normal supply HEPAs for that area). However, recycling of air between areas may be permissible provided that it passes through two exhaust HEPAs in series. The first of which is continuously monitored for integrity, and there are adequate measures for safe venting of exhaust air should this filter fail;

c) (c) air from manufacturing areas used for the handling of exotic organisms should be vented through 2 sets of HEPA filters in series. And that from production areas not re-circulated;

г) (d) a system for the collection and disinfection of liquid effluents including contaminated condensate from sterilisers, biogenerators, etc. Solid wastes, including animal carcasses, should be disinfected, sterilised or incinerated as appropriate. Contaminated filters should be removed using a safe method;

д) (e) changing rooms designed and used as air locks, and equipped with washing and showering facilities if appropriate. Air pressure differentials should be such that there is no flow of air between the work area and the external environment or risk of contamination of outer clothing worn outside the area;

e) (f) an air lock system for the passage of equipment, which is constructed so that there is no flow of contaminated air between the work area and the external environment or risk of contamination of equipment within the lock. The air lock should be of a size which enables the effective decontamination of the surface of the materials passed through it. Consideration should be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective.

ж) (g) in many instances, a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items.

(12) Equipment passes and changing rooms should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time. Changing rooms should be supplied with air filtered to the same standard as that for the work area, And equipped with air extraction facilities to produce an adequate air circulation independent of that of the work area. Equipment passes should normally be ventilated in the same way, but unventilated passes, or those equipped with supply air only, may be acceptable.

19. (13) Production operations such as cell maintenance, media preparation, virus culture, etc. likely to cause contamination should be performed in separate areas. Appropriate precaution is required when working with animals and products of animal origin.

20. (14) Production areas where biological agents particularly resistant to disinfection (e.g. spore-forming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.

21. (15) With the exception of blending and subsequent filling operations, microorganisms of single species only should be handled at a time within an area.

22. (16) Production areas should be designed to permit disinfection between campaigns, using validated methods.

23. (17) Production of microorganisms may take place in controlled areas provided it is carried out in totally enclosed and thermally sterilised equipment, all connections being also thermally sterilised after making and before breaking. It may be acceptable for connections to be made under local laminar air flow provided these are few in number and proper aseptic techniques are used and there is no risk of leakage. The sterilisation parameters used before breaking the connections must be validated for the organisms being used. Different products may be placed in different biogenerators, within the same area, provided that there is no risk of accidental cross-contamination. However, organisms generally subject to special requirements for containment should be in areas dedicated to such products.

24. (18) Animal facilities where animals intended or used for production are accommodated, should be provided with the appropriate containment and/or clean area measures. Such premises should be separated from other animal accommodation. Premises containing animals used for quality control of products (including those using pathogenic microorganisms) should be appropriately isolated.

(19) Only authorized personnel with permit may have access to production areas. It is necessary to have a clear and concise instruction on mode of access to production areas. It is recommended to hang out the instruction on the wall.

26. (20) The documentation describing production facilities should be available as part of the Site Master File.

27. The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) so that the designation and conditions of use of all the rooms are correctly identified as well as the biological agents which are handled in them. The directions of movement of personnel and products should also be clearly indicated. The animal species accommodated in the animal houses or otherwise on the site should be identified. The activities carried out in the vicinity of the site should also be indicated.

28. Plans for isolated and (or) clean rooms and areas should include a description of the ventilation system, indicating the locations of air inflow and exhaust, filters used and their specifications, rates of air exchange and pressure drops. It is necessary to specify between which rooms the differential pressure is monitored using pressure gauges.

#### IV. EQUIPMENT

(21) The equipment used shall be designed and assembled in such a way as to meet the requirements for the manufacture of each product.

30. Before being put into operation the equipment should be qualified and validated and subsequently be regularly maintained and validated.

31. (22) The equipment must provide a should ensure satisfactory primary containment of biological agents. Where appropriate, the equipment should be designed and constructed as to allow easy and effective decontamination and (or) sterilisation.

32. (23) Closed equipment used for the primary containment of the biological agents should be designed and constructed as to prevent any leakage or the formation of droplets and aerosols.

33. The gas inlets and outlets should be protected in such a way as to provide an adequate containment, for example by using sterilising hydrophobic filters.

34. For supply or disposal of materials, a sterilisable closed system or appropriate conditions of laminar air flow should be used.

35. (24) If necessary, the equipment should be sterilised before use, preferably with dry steam under pressure. Other methods are applicable if steam sterilisation cannot be used because of the nature of the equipment. During processing it is important not to overlook such equipment as centrifuges and water baths.

36. Equipment used for purification, separation or concentration should, at least, be sterilised or disinfected when switching from one product to another. It is necessary to investigate influence of sterilisation methods on the efficiency and validation status of equipment in order to determine its life span.

37. All methods of sterilisation should be validated.

38. (25) The design of the equipment should prevent any mix-up between different organisms or products. Pipelines, valves and filters shall be labelled in accordance with their function.

39. Separate incubators should be used for containers with infected and uninfected materials, and also,

generally, for different organisms or cells. Keeping of more than one organism or cell type in one incubator will be acceptable only if adequate steps are taken to seal, surface decontaminate and segregate the containers. Vessels with cultures, etc. should be individually labelled. Cleaning and disinfection of these vessels and incubators can be difficult and should require special attention.

40. Equipment used for the storage of biological agents or products should be designed and used in such a manner as to prevent any possible mix-up.

41. All stored samples must be clearly and unambiguously labeled and kept in containers that are protected from leakage. Stock cultures of cells and organisms should be stored in specially designed equipment.

42. (26) Some types of equipment (for example, equipment requiring temperature control) should be equipped with recording devices and / or alarm systems. In order to avoid breakdowns, the manufacturer should implement a preventive maintenance system, together with the analysis of trends in the recorded data.

43. (27) The loading of freeze-dryers should take place in a clean and (or) contained area. Unloading freeze dryers contaminates the immediate environment. Therefore, for single-ended freeze dryers, the clean room should be decontaminated before a further manufacturing batch is introduced into the area, unless this contains the same organisms. Double door freeze dryers should be sterilised after each production cycle, unless opened into a clean area.

44. Sterilisation of freeze drying plants should be carried out in accordance with [items 35- 37](#) of this Annex. In the case of campaign working, they should at least be sterilised after each campaign.

#### V. ANIMALS AND ANIMAL HOUSES

45. (28) The general requirements for animal quarters, care and quarantine are given in the relevant regulatory legal acts of the Russian Federation.

46. (29) Animal houses should be separated from the other production premises. They should be suitably designed in accordance with the necessary requirements.

47. (30) The sanitary status of the animals used for production should be defined, monitored, and recorded. Some animals should be handled as defined in the specific regulations of the Russian Federation (e.g. Specific Pathogens Free flocks).

48. (31) Animals, biological agents, and tests carried out should be the subject of an identification system, so as to prevent any risk of confusion and to control all possible hazards.

#### VI. DISINFECTION. DISPOSAL OF WASTE

49. (32) Disinfection and/or wastes and effluents disposal may be particularly important in the case of manufacture of immunobiological products. Careful consideration should therefore be given to procedures and equipment aiming at avoiding environmental contamination as well as to their validation or qualification.

#### VII. MANUFACTURE

50. (33) Because of the wide variety of products, the large number of stages in the production of immunobiologicals for veterinary use and the nature of biological processes, special attention must be paid to strict adherence to validated processes, constant monitoring of production at all stages and to in-process controls. Additionally, special consideration should be given to starting materials, media and the use of seed lot (inoculum) systems.

#### VIII. STARTING MATERIALS

51. (34) Requirements for starting materials should be specified in the specifications. Specifications should contain data on the supplier, method of production, its location and species of animals from which the starting materials are obtained, as well as the methods of its control. Microbiological methods are particularly important.

52. (35) The results of the tests on starting materials shall comply with the specifications. If tests take a long time (for example, specific-pathogen free (SPF) eggs (embryos) of birds), it may be necessary to starting materials prior to obtaining analytical test results. In these cases, obtaining a permit for release of finished products depends on the positive results of testing starting materials.

53. (36) Particular attention should be paid to data on the supplier's quality assurance system when assessing the conformity of sources of raw materials and materials as well as the amount of tests required when conducting incoming quality control.

54. (37) If possible, it is necessary to sterilise raw materials by thermal method. It is also possible to use other validated methods, for example, ionizing radiation.

#### Media

55. (38) The ability of media to support the desired growth should be properly validated in advance.

56. (39) It is preferable that the media be sterilised in situ or on line. The method of thermal sterilisation is preferred. Gases, media, acids, alkalis, defoamers and other substances introduced into the sterile bioreactor must be sterile.

#### Seed lot (inoculum) and cell bank system

57. (40) In order to prevent undesirable changes in properties that might ensue from repeated subcultures or multiple generations, the production of immunobiologicals for veterinary use derived from cultures of microorganisms, cultures of cells, tissues or propagation in embryos and animals must be based on inocula and cell banks system.

58. (41) The number of generations (doublings, passages) between inoculum or cell bank and the finished product must meet the requirements of the dossier or the Marketing Authorisation.

59. (42) Inocula and cell banks should be distinguished and tested for contaminants. Acceptance criteria should be established for new seed lots (inocula). Inocula and cell banks should be created, stored and used in such a way as to minimise the risk of their contamination or any change. When creating inocula or cell banks, no other living or infectious material (e.g. virus or cell lines) shall be handled simultaneously in the same area or by the same personnel.

60. (43) Establishment of the seed lot and cell bank should be performed in a suitable environment to protect the seed lot and the cell bank, as well as personnel working with them and external environment control.

61. (44) The origin, form and storage conditions of seed material should be described in full in the relevant documentation. Evidence of the stability and recovery of the seeds (inocula) and cells should be provided. Storage containers should be hermetically sealed, clearly labeled and stored at an appropriate temperature. Storage conditions shall be properly monitored. An inventory should be kept and each container accounted for.

62. (45) Only authorised personnel should be allowed to handle the material. The work must be carried out under control of the responsible person. Different inocula and cell banks should be stored in such a way as to avoid confusing or cross-contamination. It is desirable to split theseed lots and cell banks, and to store different parts separately to avoid their complete loss.

#### Operating principles

63. (46) During processes, the formation of droplets or foam should be avoided or minimized. Centrifugation or blending processes that can lead to the droplet formation should be carried out in appropriate contained containers or in clean and / or contained areas in order to prevent the transfer of living organisms.

64. (47) Accidental spillage of liquids, especially those containing living organisms, must be quickly and safely disposed of. Validated decontamination procedures should be used for each type of microorganism. When different strains of single bacteria species or very similar viruses are involved, the decontamination procedure can

be validated with respect to only one of them unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

65. (48) Operations involving the passage of materials such as sterile media, cultures or products should be carried out in pre-sterilised closed systems. If this is not possible, the material transfer operations should be carried out under laminar airflow.

66. (49) The addition of media or cultures to bioreactors and other vessels should be carried out under carefully controlled conditions to avoid contaminants introduction. When adding cultures, it is necessary to carefully check the correct junction of the vessels.

67. (50) If necessary (for example, when two or more fermentors are located in the same area), the sampling and additions ports and the connectors must be steam sterilised (after connection, before the product is dispensed and before disconnection). In other cases, chemical disinfection of the inlet openings and the protection of the connections under the laminar airflow are permitted.

68. (51) Equipment, glassware, the external surfaces of product containers and other such materials must be disinfected before transfer from a contained area using a validated method. A special problem can be caused by the maintenance of documentation for a batch of products. Only the absolute minimum required to allow operations in accordance with the requirements of this [GMP](#), must enter the work area and leave it. If obviously contaminated, such as by spills or aerosols, or if the organism involved is an exotic, the paperwork must be adequately disinfected through an equipment pass, or the information transferred out by such means as photocopy or fax.

69. (52) Liquid or solid wastes, such as eggshell after selection of material from eggs, disposable culture bottles, unwanted cultures or biological agents, must be sterilised or disinfected before they are removed from contained area. In some cases, other methods are considered acceptable, for example, use of sealed containers or pipelines.

70. (53) Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only articles and materials concerned with production are introduced. There should be a system which ensures that articles and materials entering a room are reconciled with those leaving so that their accumulation within the room does not occur.

71. (54) Heat stable articles and materials entering a clean area or clean/contained area should do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an air-lock with interlocked doors where they are disinfected. Sterilisation of articles and materials elsewhere is acceptable provided that they are double wrapped and enter through an airlock with the appropriate precautions.

72. (55) The manufacturer must take appropriate precautions to avoid contamination or confusion of cell or microbial cultures during the incubation period. It is necessary to approve the incubators cleaning and disinfection method. Containers in incubators must be clearly and carefully labeled.

73. (56) The work with single living biological agent should be run at the same time in single premise, except for operations of mixing and subsequent filling, or using completely closed systems. In the intervals between operations with various living biological agents, production facilities must be disinfected.

74. (57) Products should be inactivated by the addition of inactivant accompanied by sufficient agitation. After that, the mixture should be transferred to a second sterile vessel, except when the shape and size of the vessel allow to easily turn and shake it so that all internal surfaces are wetted by the final mixture of culture and inactivator.

75. (58) Vessels containing the inactivated product shall not be opened. It is not allowed to take samples from such vessels in areas where living biological agents are contained. All post-treatment of inactivated products must be carried out in clean areas of classes A and B or in closed equipment specifically designed for inactivated products.

76. (59) Special attention should be paid to the validation of methods for sterilisation, disinfection, removal of

viruses and their inactivation.

77. (60) The filling shall be carried out for as short a period of time period as possible after the completion of the production operations. Before the start of the filling operation, containers with bulk products shall be hermetically sealed, appropriately labeled and stored under the specified temperature conditions.

78. (61) The manufacturer shall develop a system to ensure the integrity and tightness of the packages after filling.

79. (62) Vials containing live biological agents should be closed with caps in such a way as to exclude the possibility of contamination by other products or penetration of living agents into other areas or into the external environment.

80. (63) Between the filling of primary packages, their labeling and packing for various reasons, a certain period of time may pass. The manufacturer must approve procedures describing the storage of unlabeled containers to prevent their confusing and ensure proper storage conditions. Particular attention should be paid to storage of thermolabile and photosensitive products. The manufacturer must establish the storage temperature requirements.

81. (64) For each stage of production, the yield of product should be reconciled with that expected from that process. Any significant discrepancies should be investigated.

## IX. QUALITY CONTROL

82. (65) In-process controls play a specially important role in ensuring the consistency of the quality of biological medicinal products. The types of control that are crucial to quality assessment (eg, virus removal), but which can not be carried out with respect to finished products, should be performed at one of the previous stages of production.

83. (66) It may be necessary to retain samples of intermediate products in sufficient amount and under appropriate storage conditions to allow repetition or confirmation of a batch control.

84. (67) There may be a need for continuous monitoring of parameters during a production process (for example, continuous monitoring of physical parameters during fermentation).

85. (68) During the continuous cultivation of biological products, special requirements for the organization of quality control of products must be observed.

Annex No. 6  
to Good Manufacturing  
Practice

## MANUFACTURE OF MEDICINAL GASES

### I. PRINCIPLE

1. This Annex provides guidance on the manufacture of gases as active substances (API) and the manufacture of gases for medical use (hereinafter - medicinal gases). The manufacture of medical gases being medicinal products, should be carried out in accordance with the appropriate regulatory legal acts of the Russian Federation.

2. The Annex does not cover the manufacture and handling of medicinal gases in hospitals unless this is considered industrial preparation or manufacturing.



3. The distinction between the manufacture of API and the manufacture of medicinal products must be clearly defined in each Marketing Authorisation dossier. Normally, the production and purification steps of the gas belong to the field of manufacture of active substances. Gases relate to medicinal products from the moment of the first conservation of gas intended for such use.

4. In the exceptional cases of continuous processes where no intermediate storage of gas between the manufacture of the active substance and the manufacture of the medicinal product is possible, the whole process (from starting materials of active substance to medicinal finished product) should be considered as belonging to the pharmaceutical field. This should be clearly stated in the Marketing Authorisation dossier.

## II. MANUFACTURE OF ACTIVE SUBSTANCE GASES

5. Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (as for example in an air separation plant).

6. (1) The Manufacturer shall carry out the processes for obtaining gases by the above methods in accordance with the requirements of IV of this Regulation, with [Chapter IV](#) of this Practice. In this case,

a) (a) requirements for starting materials for active substances ([para. 400 - 421](#) of GMP) are not applicable to the production of active substance gases by air separation (however, the manufacturer must ensure that the quality of the of ambient air is suitable for the established process and changes in ambient air quality will not affect the quality of active substance gas);

b) (b) the requirements regarding on-going stability studies of active substances gases ([paragraphs 497 - 503](#) of this Practice), which are used to confirm storage conditions and expiry/retest dates ([paragraphs 487 - 490](#) of this GMP), do not apply in case initial stability studies have been replaced by bibliographic data;

c) (c) the requirements regarding reference/retention samples ([paragraphs 508 - 510](#) of this GMP) do not apply to active substance gases, unless otherwise specified by the regulatory legal acts of the Russian Federation.

7. (2) The production of active substance gases through a continuous process (for example, air separation) should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.

8. (3) (a) (a) transfers and deliveries of active substance gases in bulk should comply with the same requirements as those mentioned below for the medicinal gases ([items 29 - 31](#) of this Annex);

(b) The filling of active substance gases into cylinders or mobile cryogenic vessels should comply with the same requirements as those mentioned below for the medicinal gases ([items 32 - 48](#) of this Annex), and the requirements set out in [paragraphs 450 - 469](#) of the GMP.

## III. MANUFACTURE OF MEDICINAL GASES

10. Production of medical gases, as a rule, is carried out in closed equipment. In this regard, the environmental contamination of the product is minimal. However, there is a risk of contamination or cross-contamination with other gases, especially because of the reuse of containers.

11. (4) The requirements applicable to cylinders also apply to groups (bundles) of cylinders (except storage and transportation under cover).

### Personnel

12. (5) All personnel involved in manufacture and distribution of medicinal gases should receive an appropriate GMP and quality control training, specifically applying to this type of products. Employees should be aware of the critical aspects potential hazards for patients from these products in the form of medical gases. The training programs should include the tanker lorries drivers transporting medical gases.

13. (6) Personnel employed as contractors, who may affect the quality of medical gases (for example,

personnel servicing cylinders or valves) must be adequately trained.

#### Premises and equipment

##### Premises

14. (7) Cylinders and mobile cryogenic vessels should be checked, prepared, filled and stored in areas separated from areas of work with non-medical gases. There should be no exchange of cylinders /mobile cryogenic vessels between these areas. However, it could be accepted to check, prepare, fill and store other gases in the same areas, provided they comply with the specifications of medicinal gases and that the manufacturing operations are performed according to [GMP](#) standards.

15. (8) Premises in which operations for production, testing and storage of medical gases are performed should be of sufficient size to avoid the risk of mix up. Premises should be designed to provide:

a) (a) separate marked areas for different gases;

b) (b) clear self-explanatory designation and separation of empty cylinders and (or) mobile cryogenic vessels, as well as cylinders and / or mobile cryogenic vessels at different stages of processing (for example, "waiting checking", "waiting filling", "quarantine", "certified", "rejected" "prepared deliveries").

16. Methods of separation depend on the nature, volume and complexity of the process. Separation measures can be areas with markings on the floor, partitions, barriers, signs.

17. (9) Empty cylinders and / or mobile cryogenic vessels after sorting or maintenance and filled cylinders and (or) mobile cryogenic vessels should be stored under canopies to protect them from adverse weather conditions. Filled cylinders and (or) mobile cryogenic vessels should be stored in conditions that guarantee their delivery in clean state, compatible with the environment in which they will be used.

18. (10) Specific storage conditions should be provided as required by the Marketing Authorisation (e.g. for gas mixtures where phase separation occurs on freezing).

##### Equipment

19. (11) The equipment should be designed in such a way as to ensure that the gas is filled into the appropriate container. As a rule, no connections should be between pipelines through which various gases pass. If such connections are necessary (for example, equipment used to fill with gas mixtures), the manufacturer must carry out the appropriate qualification to ensure that there is no risk of cross- contamination with different gases. In addition to this requirement, distribution manifolds must be equipped with specific connecting elements. If the regulatory legal acts of the Russian Federation establish the requirements for the use of distribution manifolds and their connections to the valves of cylinders, such requirements must be observed. The use of connections meeting different standards at the same filling site should be carefully controlled, as well as the use of adaptors needed in some situations to bypass the specific fill connection systems.

20. (12) Storage tanks and mobile tankers should only be dedicated to a single and defined quality of gas. Medical gases may be stored or transported in the same tanks as similar non-medical gases, provided that the quality of the latter is at least equivalent to the quality of medical gases, and the requirements of this [Practice](#). In such cases, quality risk management should be performed and documented by the manufacturer.

21. (13) A common system supplying gas to medicinal and non-medicinal gas manifolds is only acceptable if there is a validated method to prevent backflow from the non-medicinal gas line to the medicinal gas line.

22. (14) The manufacturer shall have a filling manifold intended for a single medical gas or for a given mixture of medical gases. In exceptional cases, filling gases used for other medical purposes on manifolds dedicated to medicinal gases may be acceptable if justified and performed under control. In these cases, the quality of non-medical gas must be at least equivalent to the quality of medical gas and the requirements of this [Practice](#) must be observed. Filling should be done by campaigns.

23. (15) Repair and maintenance of equipment (including purification and purging) should not adversely affect the quality of medical gases. Procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. Specifically it should be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records should be maintained.

24. (16) The procedure should describe the measures to be taken when a tanker is back into medicinal gas service after the transportation of non-medical gas in the conditions specified in [item 20](#) of this Annex or after maintenance operations. Such a procedure should include analytical tests.

#### Documentation

25. (17) Data included in the records for each batch of cylinders/mobile cryogenic vessels must ensure that each filled container is traceable to significant aspects of the relevant filling operations.

26. The batch records should, as appropriate, include the following:

a) (a) name of the product;

б) (b) batch number;

в) (c) date and time of the filling operation;

г) (d) personnel performing the main process stages (for example, line cleaning, materials acceptance, preparing filling lines, filling);

д) (e) reference to the number (s) of the batch(es) of gas (es) used for filling operations in accordance with [item 32](#) of this Annex, including its status (authorization to be filled);

е) (f) the equipment used (for example, the filling manifold);

ж) (g) number of cylinders and (or) mobile cryogenic vessels before the filling operation, including the identification reference of each container and and water capacity(ies);

з) (h) pre-filling operations performed ([item 41](#) of this Annex);

и) (i) key parameters that are needed to ensure correct filling at standard conditions;

к) (j) results of appropriate checks to ensure the cylinders/mobile cryogenic vessels have been filled;

л) (k) a sample of the batch label;

м) (l) specification of the finished product and results of quality control tests (including references to the current calibration status of equipment used during the tests);

н) (m) quantity of rejected cylinders and (or) mobile cryogenic vessels with their individual identification references and reason for rejection;

о) (n) details of all problems and deviations, approved authorisation for any deviation from filling instructions;

п) (o) certification statement with batch release by the Qualified Person, date and signature.

Records should be maintained for each batch of gas intended to be delivered into hospital tanks. The records should include the following information (if applicable):

a) (a) name of the product;

б) (b) batch number;

в) (c) reference to the identification number of the tank (tanker) in which the batch is certified;

г) (d) date and time of the filling operation;

personnel who filled the tank (tanker);

е) (f) reference to the supplying tanker (tank), reference to the source gas as applicable;

ж) (g) relevant details concerning the filling operation;

з) (h) specification for the finished medicinal product and the results of quality control (including references to the current condition of calibration of equipment used during the tests);

и) (i) details of all problems and deviations, approved permission for any deviation from the filling instructions;

к) (j) certification statement by the Qualified Person, with date and signature stamped.

28. If the regulatory legal acts of the Russian Federation establish special requirements for the content of the mentioned records, such requirements must be observed.

#### Production process

##### Transfer and delivery of cryogenic and liquefied gases

29. (19) Transfer of cryogenic or liquefied gases from primary storage, including controls before transfers, should be in accordance with validated procedures designed to prevent possible contamination. Transfer lines should be equipped with non-return valves or other appropriate device. Flexible connections, coupling hoses and connectors should be flushed with a suitable gas before use.

30. (20) Hoses used to fill tanks and tankers shall be equipped with product-specific connections. The use of adaptors allowing the connection of tanks and tankers should be adequately controlled.

31. (21) Deliveries of gas may be added to tanks containing the same defined quality of gas provided that a sample is tested to ensure the quality of the feed gas is acceptable. The sample may be taken from the gas to be delivered or from the receiving tank after delivery. See specific arrangements of quality control for filling of tanks retained by customers in [item 56](#) of this Annex.

##### Filling and labeling of cylinders and (or) mobile cryogenic vessels

32. (22) Before filling cylinders and mobile cryogenic vessels, a batch (batches) of gas (es) shall be identified and controlled in accordance with the specifications and approved for filling.

33. (23) in case of continuous processes, there should be adequate in-process controls to ensure that the gas complies with specifications.

34. (24) Cylinders, mobile cryogenic vessels and valves shall comply with the established technical specifications and relevant requirements of the Marketing Authorisation. They should be dedicated only for a single medical gas or to a certain mixture of medical gases. Cylinders should be colour-coded according to relevant standards. They should preferably be fitted with minimum pressure retention valves with non-return mechanism in order to provide adequate protection against contamination.

35. (25) Cylinders, mobile cryogenic vessels and valves shall be checked before first use in production and maintained in an appropriate manner. When using medical devices, their maintenance should address the instructions for cylinders, mobile cryogenic vessels and valves.

36. (26) Checks and maintenance should not adversely affect the quality and safety of the medicinal product. The water used to test cylinders with hydrostatic pressure should be at least of drinking water quality.

37. (27) As part of the checks and maintenance operations, cylinders should be subject to an internal visual inspection before fitting the valve, to make sure they are not contaminated with water or other contaminants. This operation must be performed as part of the checks and maintenance. It should be carried out:

for new cylinders first used for medical gases;

following any hydrostatic statutory pressure test or equivalent test where the valve is removed;

whenever the valve is replaced.

38. After fitting, the valve should be kept closed to prevent any contamination from entering the cylinder. If there is any doubt about the internal condition of the cylinder, the valve should be removed and the cylinder internally inspected to ensure it has not been contaminated.

39. (28) Maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medicinal product. Such contractual works must be carried out only by the contractors specified in the agreement. It is recommended to include specifications for the outsourced activities in the contracts covering such activities. The manufacturer shall inspect how the terms of the contract are fulfilled by contractors, including the conditions for compliance with the requirements of this [Practice](#).

40. (29) There should be a system to ensure the traceability of cylinders, mobile cryogenic vessels and valves.

41. (30) Checks to be performed before filling should include as follows:

a) (a) in the case of cylinders, a check, carried out according to defined procedure to ensure there is a positive residual pressure in each cylinder:

if the cylinder is fitted with a minimum pressure retention valve, when there is no signal indicating there is a positive residual pressure, the correct functioning of the valve should be checked, and if the valve is shown not to function properly, the cylinder should be sent to maintenance;

if the cylinder is not fitted with a minimum pressure retention valve, when there is no positive residual pressure the cylinder should be put aside for additional measures, to make sure it is not contaminated with water or other contaminants; additional measures could consist of internal visual inspection, followed by cleaning using a validated method;

б) (b) a check to ensure that all previous batch labels have been removed;

в) (c) a check that any damaged product labels have been removed and replaced;

г) (d) a visual external inspection of each cylinder, mobile cryogenic vessel and valve in order to detect blowholes, welding burns, other damages and oil contamination, cleaning should be done, if necessary;

д) (e) a check of each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas being filled;

е) (f) a check of the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested);

ж) (g) a check of the cylinders or mobile cryogenic vessels to ensure that any tests required in accordance with the regulatory legal acts of the Russian Federation, (e.g. hydrostatic pressure test or equivalent for cylinders) have been conducted and are still valid;

з) (h) a check to determine that each cylinder is colour-coded as specified in the Marketing Authorisation (colour-coding according to the established requirements).

42. (31) A batch size should be defined for filling operations.

43. (32) Cylinders that have been returned for refilling should be prepared with care in order to minimise the risks of contamination, in line with the procedures defined. The procedures including evacuation and / or purging operations should be validated. For compressed gases, a maximum theoretical impurity of 500 ppm v/v should be obtained for a filling pressure of 200 bar at 15°C. Equivalent values are determined for another pressure.

44. (33) In order to minimize the contamination risk, mobile cryogenic vessels returned to refueling should be carefully prepared in accordance with approved procedures. In particular, mobile vessels in which there is no residual pressure should be prepared using a validated method.

45. (34) There should be appropriate checks to ensure that each cylinder and / or mobile cryogenic vessel has been properly filled.

46. (35) Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamper evident seal (see [item 47](#) of this Annex). The control method used should not lead to contamination of the surface of the valve outlet. If possible, such monitoring should be carried out after any quality sample is taken.

47. (36) After filling, cylinders valves should be fitted with covers to protect the outlets from contamination. Tamper-evident seals shall be installed on the cylinders and mobile cryogenic vessels.

48. (37) Each cylinder or mobile cryogenic vessel shall be labelled. The batch number and expiry date maybe be on a separate label.

49. (38) In the case of medicinal gases produced by mixing two or more different gases (in-line before filling or directly into the cylinders), the mixing process should be validated to ensure that the gases are properly mixed in every cylinder and that the mixture is homogeneous.

#### Quality Control

50. (39) Each batch of medical gas (cylinders, mobile cryogenic vessels, hospital tanks) should be tested in accordance with established requirements, In accordance with the requirements of the Marketing Authorisation and certified.

51. (40) Unless otherwise specified in the procedures, the sampling plan and the amount of tests to be conducted should meet the following requirements for cylinders:

a) (a) In the case of a single medicinal gas filled into cylinders via a multi-cylinder manifold, the gas from at least one cylinder from each manifold filling cycle should be tested for identity and assay each time the cylinders are changed on the manifold;

b) (b) In the case of a single medicinal gas filled into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle should be tested for identity and assay. An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment, and batch of gas to be filled;

b) (c) In the case of a medicinal gas produced by mixing two or more gases in a cylinder from the same manifold, the gas from every cylinder should be tested for assay and identity of each component gas. For excipients (if any), an authenticity test can be performed on one cylinder per manifold filling cycle (or per uninterrupted filling cycle). Fewer cylinders may be tested in case of validated automated systems;

r) (d) Premixed gases should follow the same principles as single gases when continuous in-line testing of the mixture to be filled is performed.

52. Premixed gases should follow the same principle as gases produced by mixing gases in the cylinders when there is no continuous in-line testing of the mixture to be filled.

53. Water content tests should be carried out unless otherwise justified by the manufacturer.

54. Other sampling and testing techniques may be used that provide at least equivalent level of quality assurance may be justified.

55. (41) Unless different provisions are required, final testing on mobile cryogenic vessels should include a test for assay and identity on each vessel. Testing by batches should only be carried out if it has been demonstrated that the critical quality attributes of the gas remaining in each vessel before refilling have been maintained.

56. (42) Cryogenic vessels retained by customers (hospital tanks or home cryogenic vessels), which are refilled in place from dedicated tankers do not need to be sampled after filling provided that a certificate of analysis on the contents of the tanker accompanies the delivery. However, it should be demonstrated by the manufacturer that the specification of the gas in the vessels is maintained over the successive refillings.

57. (43) Reference and retention samples are not required, unless otherwise specified.

58. (44) On-going stability studies are not required in case initial stability studies have been replaced by bibliographic data from the scientific literature.

#### Transportation of packaged gases

59. (45) Filled gas cylinders and mobile cryogenic vessels should be protected during transportation. In particular, they they are delivered to customers in a clean state compatible, with environment in which they will be used.

#### IV. TERMS AND DEFINITIONS

60. For the purposes of this Annex, in addition to the terms and definitions provided for in [Chapter II](#) of this GMP, the following basic concepts are also used:

home cryogenic vessel - a mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at patients' home;

gas - any substance or a mixture of substances that is completely gaseous at 1.013 bar and +20°C or has vapour pressure exceeding 3 bar at +50°C;

active substance gas - any gas intended to be an active substance for a medicinal product;

cylinder group (bundle) - an assembly of cylinders that are fastened together, interconnected through a distribution manifold, transported and used as a single unit;

hydrostatic pressure test - test performed as required by national or international regulations, in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure;

valve - device for opening and closing the container;

residual pressure retention valve - a valve mounted on the cylinder to maintain pressure above atmospheric to prevent contamination of the internal space of the cylinder;

container - cryogenic vessel (tank, tanker, or mobile cryogenic vessel of another type), cylinder, cylinder bundle or any other package that is in direct contact with medical gas;

cryogenic gas- a gas which liquefies at 1.013 bar at temperatures below minus 150 °C;

maximum theoretical impurity - gaseous impurity from a possible backflow that remains after the cylinder pre-treatment process before filling. The calculation of the maximum theoretical impurity level is important only for compressed gases under the assumption that these gases behave as ideal;

medicinal gas - any gas or a mixture of gases classified as medicinal products;

non-return valve - a valve that allows the flow to pass in only one direction;

evacuate - to remove residual gas from a container and (or) a system to a pressure less than 1.013 bar,

using a vacuum system;

mobile cryogenic vessel - mobile thermally insulated container designed to store substances in a liquid state. For the purposes of this Annex, the term does not include the term "tanker";

purge - to remove residual gas from a container/system by first pressurising and then venting the gas used for purging to 1.013 bar;

air separation - separation of atmospheric air into its constituent gases using fractional distillation at cryogenic temperatures;

(distribution) manifold - equipment or apparatus designed to enable one or more gas containers to be emptied and filled at the same time;

tank - static thermally insulated container for storing liquefied or cryogenic gas, also called "fixed cryogenic vessel";

vent - to remove the residual gas from a container / system down to 1.013 bar, by opening the container / system to atmosphere;

compressed gas - gas which, when packaged under pressure for transport, is entirely gaseous at all temperatures above minus 50 °C;

liquefied gas - a gas which, when packaged for transport, is partially liquid (or solid) at a temperature above minus 50 °C;

tanker - a thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.

Annex No. 7  
to Good Manufacturing  
Practice

## PRODUCTION OF HERBAL MEDICINAL PRODUCTS

### I. PRINCIPLE

1. Herbal medicinal products have a complex nature and various characteristics, for this reason, control of starting materials, storage and processing conditions is essential in their production. The starting materials for production of herbal medicinal products are herbal medicinal raw materials. Herbal medicinal raw materials should be of the required quality, and the evidence confirming this fact should be provided by the supplier of starting materials to the manufacturer of the herbal preparation. To ensure the quality of herbal medicinal raw materials, more detailed information on the method of its production (cultivation) may be required. Seed selection, cultivation and harvesting conditions are important aspects of the quality of herbal medicinal raw materials and can influence the constant high quality of the finished herbal medicinal products. For the proper cultivation and collection of plants with respect to the appropriate quality assurance system, the Guidelines on good agricultural and collection practices for Starting Materials of Herbal Origin (GACP), approved by the Committee on Herbal Medicines of the European Medicines Agency, are recommended <\*>.

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<\*> For reference: Guidelines on Good Agricultural and Wild Collection Practices for Starting Materials of Herbal Origin (GACP) is published at the website in the information and telecommunication network of the Internet: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003362.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003362.pdf)



2. This Annex applies to all starting materials of plant origin, including medicinal plant raw materials.

3. The specifics of the application of various rules, including this **GMP**, to the production of herbal medicinal products are given in Table No. 1.

Table N 1. Features of the application of **the Practice** to the production of herbal medicinal products <\*>

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<\*> This table contains extended detailed information on the section on herbal medicinal products of Table No. 1 in **Chapter IV** of this Practice.

Activity	Guidelines on good agricultural and collection practices (GACP) for herbal medicinal plants	<b>Chapter IV</b> of this Practice	<b>Chapter III</b> of this Practice
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting and drying of plants, algae, fungi, lichens and exudates <*>			
Expression from plants and distillation <*>			
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form, including packaging of a medicinal product			

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Notes:

<\*> Manufacturers should ensure that these steps are carried out in accordance with established requirements. For those initial steps, the GACP is applicable. This **Practice** apply to the production cutting and drying steps.

<\*> Regarding the expression from plants and distillation (if necessary for these activities to be an integral part of the harvesting in order to maintain the quality of the products within the approved specifications), it is acceptable that they are performed in the field provided that the cultivation is in compliance with GACP. Such circumstances should be regarded as exceptional and justified in the relevant marketing authorisation/registration dossier documents. For such activities carried out in the field, appropriate documentation, control and validation according to the principles of this **Practice** should be assured.

II. PREMISES AND EQUIPMENT

Storage areas

4. (1) Herbal medicinal raw materials must be stored in separate areas. These areas must provide adequate protection against penetration of insects and animals, especially rodents. Effective measures should be taken to prevent the spread of animals and microorganisms brought with herbal medicinal raw materials, to avoid fermentation or mold growth, as well as cross-contamination. It is necessary to use the designated areas for

quarantine of incoming herbal medicinal raw materials and such materials, allowed for use.

5. (2) Storage area must be well ventilated. The order of placement of packages should not prevent free air circulation.

6. (3) Particular attention should be paid to the cleanliness and proper maintenance of storage areas, especially where dust is generated.

7. (4) If storage of starting materials and herbal medicinal products requires special conditions for humidity, temperature and protection against light, such conditions must be ensured and controlled.

#### Production area

8. (5) When collecting samples, weighing, mixing and other operations with herbal medicinal raw materials accompanied by dust formation, special measures should be taken to maintain cleanliness, as well as to prevent cross-contamination (dust removal, allocation of dedicated premises).

#### Equipment

9. (6) Equipment, filters and other materials used in the production must be compatible with the solvent used for extraction, to prevent any excretion or undesirable absorption of substance that may affect the product.

### III. DOCUMENTATION

#### Specifications for starting materials

10. (7) Manufacturers of herbal medicinal products must ensure that they use only the herbal medicinal raw materials that are produced in accordance with this [Practice](#) (taking into account [Table No. 1](#) of this Annex) and the Marketing Authorisation. It is necessary to have comprehensive documentation concerning the evaluation of suppliers of starting materials of herbal origin, carried out by, or on behalf of the herbal medicinal product manufacturer. Audit trails for herbal medicinal raw materials are fundamental to the quality of the starting materials. The manufacturer should ensure that the suppliers of herbal medicinal raw materials or the herbal medicinal products work in accordance with the GACP.

11. (8) In order to comply with the requirements set out in [paragraphs 92 - 134](#) of this Practice, the specification for herbal medicinal raw materials or herbal medicinal products must include:

the binomial scientific name of the plant (genus, species, subspecies and (or) varieties, as well as the author (for example, Linnaeus); other information (for example, cultivar name, chemotypic variety) should also be provided, as appropriate;

detailed information on the source of the plant (in particular, country or region of origin (growth or cultivation), time and method of harvesting, probably used pesticides, possible radioactive contamination);

which part(s) of the plant(s) is (are) used;

information on the drying method if dried plants are used;

description of herbal medicinal raw materials, as well as its macro- and microscopic examination data;

data on necessary tests for authenticity, including, if necessary, tests for authenticity for ingredients with known therapeutic activity or markers. Specific distinctive tests are required where an herbal substance is liable to be adulterated/ substituted. To determine the authenticity, a reference authentic specimen must be available for comparison;

moisture content in herbal medicinal raw materials, determined in accordance with the requirements of the State Pharmacopoeia of the Russian Federation;

assay of constituents of known therapeutic activity or, where appropriate, markers, as well as methods suitable for determining possible pesticide contamination and limits accepted in accordance with the requirements of the State Pharmacopoeia of the Russian Federation, or, in the absence thereof, with appropriate validated method, unless otherwise justified;

Test methods in order to determine fungal and (or) microbial contamination, including aflatoxins, other mycotoxins and parasite infestation, and permissible limits, when appropriate;

Test methods for toxic metals, as well as possible contaminants and impurities, if necessary;

Test methods for foreign materials, if necessary;

Other types of control in accordance with the requirements of the State Pharmacopoeia of the Russian Federation.

12. Any treatment performed to reduce fungal and (or) microbial contamination or other invasion should be documented. It is necessary to have specifications and procedures that should include detailed information about the processing and testing, as well as limits for residual contamination.

#### Instructions

13. (9) The instructions shall describe various operations performed with herbal medicinal raw materials, such as cleaning, drying, grinding and sieving, as well as data on the duration and temperature of drying and methods used to control pieces or particles fragments size.

14. (10) There should be approved instructions and records that ensure that each container with herbal medicinal raw materials is carefully examined to detect any adulteration/ substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand) or any signs of decay.

15. (11) Instructions shall contain methods for the removal of foreign materials and appropriate methods for purification and (or) selection of materials of plant origin prior to storage as an authorized herbal medicinal raw material or before commencement of production.

16. (12) The instructions for the production of herbal medicinal products should include details of the solvent, duration and temperature of extraction, information on any concentration steps and methods used.

#### IV. QUALITY CONTROL

##### Sampling

17. (13) As herbal medicinal raw materials are inherently heterogeneous, sampling from it should be carried out by personnel with adequate special skills. Each lot should be identified by its own documentation.

18. (14) It is necessary to keep control samples of herbal medicinal raw materials. When powders are produced, it is necessary to preserve samples of unmilled herbal medicinal raw materials.

19. (15) Personnel conducting quality control should have adequate training and experience in working with herbal medicinal raw materials, intermediates or herbal medicinal products to be able to test for authenticity and presence of impurities, identify fungi growth, contamination with granary pests in the obtained starting materials, detect heterogeneity of raw materials.

20. (16) The authenticity and quality of herbal medicinal raw materials, intermediates and herbal medicinal products must be determined in accordance with the requirements of the State Pharmacopoeia of the Russian Federation, regulatory documentation or regulatory document.

## SELECTION OF STARTING MATERIALS AND PACKAGING MATERIALS

### I. PRINCIPLE

1. Sampling is an important operation, in which only a small fraction of a batch is selected. Valid conclusions regarding the whole batch can not be based on tests conducted on non-representative samples. Proper sampling is an integral part of the pharmaceutical quality system. The rules for sampling are set out in [paragraphs 214 - 217](#) of this Practice. This Annex contains additional requirements for the sampling of starting materials and packaging materials.

### II. PERSONNEL

2. (1) Personnel conducting sampling should receive initial and on-going regular training in the disciplines relevant to correct sampling. Such training should include:

- order of sampling;
- written sampling procedure approved by the manufacturer;
- methods and equipment used in sampling;
- risk of cross-contamination;
- precautions to be taken with regard to unstable and (or) sterile substances;
- importance of considering the visual appearance of materials, packages and labels;
- the importance of documenting any unforeseen or unusual circumstances.

### III. STARTING MATERIALS

3. (2) The identity of a complete batch of starting materials can normally only be ensured when individual samples are taken from all the containers and identity tests are carried out for each sample. It is allowed to take samples only from a part of the containers if a validated procedure has been developed to ensure that no single container with starting materials has been incorrectly labelled.

4. (3) During this validation, at least the following aspects must be taken into account:

data on the manufacturer and supplier (their type and current status), as well as their understanding of the requirements of this [Practice](#);

availability of a quality assurance system in the starting materials manufacturer;

the manufacturing conditions under which the starting materials are produced and controlled;

the nature and properties of the starting materials and medicinal products for the production of which they will be used.

5. Under such a system, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be acceptable for:

starting materials coming from a single product manufacturer or site;

starting materials coming directly from manufacturer or in a container sealed by the manufacturer, where

there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

6. It is improbable that a procedure could be satisfactorily validated for:

starting materials supplied by intermediaries, when the manufacturer is unknown or is not audited;

starting materials used for production of parenteral drugs.

7. (4) The quality of a batch of starting materials may be evaluated by selecting and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken to obtain a representative sample should be determined statistically and indicated in the sampling plan. The number of individual samples that can be mixed to form a composite sample should also be determined, taking into account the nature of raw material, supplier information and homogeneity of the composite sample.

#### IV. PACKAGING MATERIALS

8. (5) The sampling plan for packaging materials should consider at least the following: the quantity received, the quality required, the nature of the material (for example, primary packaging materials and / or printed packaging materials), production methods, and information on the quality assurance system of the manufacturer of packaging materials, based on audits. The number of samples taken should be determined statistically and indicated in the sampling plan.

Annex No. 9  
to Good Manufacturing  
Practice

### PRODUCTION OF LIQUIDS, CREAMS AND OINTMENTS

#### I. PRINCIPLE

1. Liquids, creams and ointments are especially susceptible to microbial and other contamination. Therefore, special precautions should be taken to prevent any contamination.

#### II. PREMISES AND EQUIPMENT

2. (1) The use of closed systems for processing and transfer is recommended in order to protect the product from contamination. The production areas where the products or open clean containers are exposed should normally be effectively ventilated by filtered air.

3. (2) The design and location of reactors, containers, pipelines and pumps should provide for the convenience of cleaning them and, if necessary, sanitizing. In particular, the design of equipment should include a minimum of dead-legs or sites where residues can accumulate and promote multiplication of microorganisms.

4. (3) The use of glass apparatus should be avoided wherever possible. High quality stainless steel is often the material of choice for parts of the equipment coming in contact with the products.

#### III. MANUFACTURE

5. (4) The chemical and microbiological quality of water used in production should be specified and monitored. To avoid the risk of multiplying microorganisms, maintenance of water treatment systems should be properly organized. After any chemical sanitization of water treatment systems, a validated flushing procedure should be followed to ensure that the sanitising agent has been effectively removed.

6. (5) The quality of the raw materials obtained in large-capacity tanks must be checked before they are transferred to bulk storage tanks.

7. (6) It is necessary to control transfer of raw materials through pipelines to ensure that they are delivered to the right place.

8. (7) Materials likely to shed fibres or other contaminants, like cardboard or wooden pallets, should not enter the areas where products or clean containers are exposed.

9. (8) Care should be taken to maintain the homogeneity of mixtures, suspensions and other bulk products, during filling. Processes of mixing and packing must undergo validation. Particular attention must be paid to ensuring homogeneity of the mixture at the beginning, after the stops and at the end of the filling.

10. (9) If the finished product is not immediately packaged, it is necessary to set the maximum allowable time before its packaging, as well as the appropriate storage conditions, which must be strictly observed.

Annex No. 10  
to Good Manufacturing  
Practice

## MANUFACTURE OF PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION

### I. PRINCIPLE

1. Production of pressurised aerosol products for inhalation with metering valves intended for inhalation requires special attention due to the specific nature of this dosage form. It should be carried out under conditions that minimize contamination by microorganisms and particles. It is also very important to ensure the quality of the valve parts, and in the case of suspensions, their uniformity.

### II. GENERAL

2. (1) As a rule, two methods of production and filling are used:

a) (a) two-shot system (pressure filling): A pharmaceutical substance is suspended in a high boiling propellant, the dose of the suspension is supplied to a container, the valve is inserted and crimped on, and the lower boiling point propellant is injected through the valve stem to make up a finished medicinal product. Therefore, the suspension of active ingredient in propellant is kept cool to reduce evaporation loss;

b) (b) one-shot process (cold filling): the pharmaceutical substance is suspended in a mixture of propellants. The suspension is held either under high pressure or at a low temperature, or both, then filled directly into the container in one shot.

### III. PREMISES AND EQUIPMENT

3. (2) If possible, production and filling, must be carried out in closed systems.

4. (3) Where products or clean components are exposed, the area should be fed with filtered air and should comply with the requirements of at least a Grade D environment. The area should be entered through air locks.

### IV. PRODUCTION AND QUALITY CONTROL

5. (4) Metering valves for aerosols are more complex than most devices used in the pharmaceutical industry. This should be taken into account in the specifications for them, as well as for sampling and testing. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

6. (5) All liquids (including liquid or liquefied pressurized gaseous propellants) shall be filtered to remove particles larger than 0.2 µm. Where possible, additional filtration is recommended immediately before filling.

7. (6) Containers and valves must be cleaned in accordance with a validated procedure appropriate to the use of the product to ensure the absence of contamination, such as contamination with fabrication aids (eg, lubricants), or microbial contamination. After cleaning, the valves should be stored in clean closed containers, and precautions should be taken to avoid contamination during subsequent operations, for example, when sampling. Packages should be delivered to the filling line in clean condition or cleaned on the line just before filling.

8. (7) Precautions should be taken to ensure uniformity of suspensions at the point of fillthroughout filling process.

9. (8) When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition. Therefore, 100% weight checking at each stage is often desirable.

10. (9) The control after filling shall confirm the absence of leaks. Check for leakage should be carried out so as to prevent microbial contamination or residual moisture.

Annex No. 11  
to Good Manufacturing  
Practice

## COMPUTERISED SYSTEMS

### I. PRINCIPLE

1. 1. This Annex applies to all types of computerised systems used as part of activities regulated by the requirements of this [Practice](#).

2. A computerised system is a set of software and hardware components that together perform certain functions.

3. The application should be validated, IT infrastructure should be qualified.

4. Where a computerised system replaces manual operation, this should not be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risks of the process.

### II. GENERAL

#### Risk Management (1)

5. Risk management should be applied throughout the life cycle of a computerised system taking into account patient safety, data integrity and product quality. As part of the risk management system, decisions on the extent of validation tests and data integrity controls should be based on a justified and documented risk assessment of the computerised system.

#### Personnel (2)

6. It is necessary to maintain close cooperation between all relevant personnel involved in the process, such as process owner, system owner, qualified persons and IT personnel. All personnel must have appropriate qualifications, level of access and defined responsibilities to carry out the duties assigned to them.

#### Suppliers and service providers (3)

7. (3.1) When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system, or related service or for data processing, formal agreements must exist between the manufacturer and the specified third parties. Such contracts should include clear statements of the responsibilities of third parties for the proper performance of their duties.

8. (3.2) The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.

9. (3.3) The documentation accompanying commercially off-the-shelf software products should be reviewed by qualified person the manufacturer's employees to check that user requirements are fulfilled.

10. (3.4) Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.

### III. THE PROJECT PHASE

#### Validation (4)

11. (4.1) The validation documentation and reports should cover the relevant steps of the life cycle of a computerised system. The manufacturer should be able to justify their standards, protocols, acceptance criteria, procedures and records based on risk assessment.

12. (4.2) The validation documentation shall include change control records (if applicable) and reports on any deviations identified during the validation process.

13. (4.3) An up to date listing of all relevant systems and their functionality, which is subject to the requirements of this [Practice](#).

14. For critical systems an up to date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.

15. (4.4) User Requirements Specifications should describe the required functions of the computerised system on the basis of a documented risk assessment and impact in terms of compliance with this [Practice](#). User requirements should be traceable throughout the life cycle of the computerised system.

16. (4.5) The manufacturer shall take all measures reasonable steps, to ensure that the computerised system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.

17. (4.6) For the validation of bespoke or customised computerised systems in accordance with the requirements of the customer, there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of a computerised system.

18. (4.7) Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.

19. (4.8) If data are transferred to another data format or system, validation should include checks that data are not altered in value and meaning during this migration process.



#### IV. OPERATION PHASE

##### Data (5)

20. Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for correct and secure data entry and processing in order to minimize risks.

##### Accuracy Checks (6)

21. For critical data entered manually, it is necessary to provide an additional check on the accuracy of data. This check may be done by a second operator or by validated electronic means. Criticality and potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management system.

##### Data Storage (7)

22. (7.1) Data should be secured by both physical and electronic means from damage. Stored data should be checked for accessibility, readability and accuracy. Access to data must be ensured throughout the retention period.

23. (7.2) Regular back-ups of all relevant data should be done. Integrity and accuracy of backups, and the ability to restore the data, should be checked during validation and monitored periodically.

##### Printouts (8)

24. (8.1) It should be possible to obtain clear printed copies of electronically stored data.

25. (8.2) For records supporting batch release, it shall be possible to generate printouts indicating if any of the data has been changed since the original entry.

##### Audit trails (9)

26. Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all significant changes and deletions related to [Practice](#) (the system generated "audit trail"). For change or deletion of [GMP](#)- relevant data the reason should be documented. Audit trails should be available and convertible to a generally intelligible form, and regularly reviewed.

##### Change and Configuration Management (10)

27. Any changes to the computerised system, including system configuration, should only be made in a controlled manner in accordance with the established procedure.

##### Periodic evaluation (11)

28. Computerised systems should be periodically evaluated to confirm that they remain in a validated state and compliant with the requirements of this [Practice](#). Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, update history, performance, reliability, security, and validation status reports.

##### Security (12)

29. (12.1) Physical and/or logical controls should be in place to restrict access to a computerised system only for authorised persons. Appropriate ways to prevent unauthorised entry to the system can include the use of keys, pass cards, personal codes with passwords, biometric data, restricted access to computer equipment and data storage areas.

30. (12.2) The extent of security controls depends on the criticality of the computerised system.

31. (12.3) Creation, change, and cancellation of access rights should be recorded.

32. (12.4) Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data, including date and time.

#### Incident Management (13)

33. All incidents (unforeseen events), not only system failures and data errors, must be recorded and assessed. The root cause of a critical incident should be identified and should form the basis for corrective and preventive actions.

#### Electronic signature (14)

34. Electronic records may be signed electronically. Electronic signatures are expected to:

- a) (a) have the same impact as hand-written signatures within the boundaries of the company;
- б) (b) be permanently linked to their respective record;
- в) (c) include the time and date that they were applied.

#### Batch release (15)

35. When a computerised system is used to for recording certification and batch release, the system should allow only Qualified Persons to certify the release of the batches, and it should clearly identify and record the person releasing or certifying the batches. These actions should be performed using an electronic signature.

#### Business continuity (16)

36. For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for these processes in the event of system breakdown (for example, manual or alternative system). The time required to bring the alternative arrangements into use should be based on risks and appropriate for a particular system and business process it supports. These arrangements should be adequately documented and tested.

#### Archiving (17)

37. Data may be archived. This data should be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g., computer hardware or software), then the ability to retrieve the data should be ensured and tested.

### V. TERMS AND DEFINITIONS

38. For the purposes of this Annex, the following basic concepts are also used, in addition to the terms and definitions provided for in [Chapter II](#) of this Practice:

Process owner: The person responsible for the business process;

System owner: The person responsible for the availability, and maintenance of a computerised system and for the security of the data residing on that system;

life cycle - All phases in the life of the system from initial requirements until retirement including design, specification, programming, testing, installation, operation and maintenance;

IT Infrastructure - The hardware and software, such as networking software and operation systems, which makes it possible for the application to function;

Bespoke/Customized computerised system - a computerised system individually designed to suit a specific

business process;

application - software installed on a defined platform / hardware providing specific functionality;

Commercial of the shelf software: Software commercially available, whose fitness for use is demonstrated by a broad spectrum of users.

Annex No. 12  
to Good Manufacturing  
Practice

## USE OF IONIZING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

1. The manufacturer of products which include ionizing irradiation as a integral part of its processing should also refer to regulatory legal acts of the Russian Federation giving guidance on "Ionizing radiation in the manufacture of medicinal products".

### I. INTRODUCTION

2. Ionising radiation may be used during the manufacturing process for various purposes including the reduction of bioburden and the sterilisation of starting materials, packaging components or products and the treatment of blood products.

3. There are two types of irradiation process: Gamma irradiation from a radioactive source and high energy electron irradiation (Beta radiation) from an accelerator.

4. Gamma Irradiation: two different processing modes may be employed:

a) (i) batch mode: the product is arranged at fixed locations around the radiation source and cannot be loaded or unloaded while the radiation source is exposed;

b) (ii) continuous mode: an automatic system conveys the products into the radiation cell, past the exposed radiation source along a defined path and at an appropriate speed, and out of the cell.

5. Electron Irradiation: the product is conveyed past a continuous or pulsed beam of high energy electrons (Beta radiation) which is scanned back and forth across the product pathway.

### II. RESPONSIBILITY

6. (1) Treatment by irradiation may be carried out by the pharmaceutical manufacturer or by an operator of a radiation facility under contract (a "contract manufacturer") Both of whom must hold an appropriate manufacturing authorisation (licence).

7. (2) The pharmaceutical manufacturer bears responsibility for the quality of the product including the attainment of the objective of irradiation. The contract operator of the radiation facility bears responsibility for ensuring that the dose of radiation required by the manufacturer is delivered to the irradiation container (i.e. the outermost container in which the products are irradiated).

8. (3) The required dose including justified limits will be stated in the marketing authorisation (registration dossier) for the product.

### III. DOSIMETRY

9. (4) Dosimetry is defined as the measurement of the absorbed dose by the use of dosimeters. Both understanding and correct use of the technique is essential for the validation, commissioning and control of the process.

10. (5) The calibration of each batch of routine dosimeters should be traceable to a national or international standard. The period of validity of the calibration should be stated, justified and adhered to

11. (6) The same instrument should normally be used to establish the calibration curve of the routine dosimeters and to measure the change in their absorbance after irradiation. If a different instrument is used, the absolute absorbance of each instrument should be established.

12. (7) Depending on the type of dosimeter used, due account should be taken of possible causes of inaccuracy including the change in moisture content, change in temperature, time elapsed between irradiation and measurement, and the dose rate.

13. (8) The wavelength of the instrument used to measure the change in absorbance of dosimeters and the instrument used to measure their thickness should be subject to regular checks of calibration at intervals established on the basis of stability, purpose and usage.

#### IV. PROCESS VALIDATION

14. (9) Validation is the action of proving that the process, i.e. the delivery of the intended absorbed dose to the product, will achieve the expected results. If additional requirements for validation are established by the regulatory legal acts of the Russian Federation for guidance on "the use of ionising radiation in the manufacture of medicinal products", such requirements must be observed.

15. (10) Validation should include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration.

16. (11) An irradiation process specification should include at least the following:

a) (a) details of the packaging of the product;

b) (b) the loading pattern(s) of product within the irradiation container. Particular care needs to be taken, when a mixture of products is allowed in the irradiation container, that there is no underdosing of dense product or shadowing of other products by dense product. Each mixed product arrangement must be specified and validated;

c) (c) the loading pattern of irradiation containers around the source (batch mode) or the pathway through the cell (continuous mode);

d) (d) maximum and minimum limits of absorbed dose to the product and associated routine dosimetry;

e) (e) maximum and minimum limits of absorbed dose to the irradiation container and associated routine dosimetry to monitor this absorbed dose;

f) (f) other process parameters, including dose rate, maximum time of exposure, number of exposures, number of exposure cycles, etc.

17. When irradiation is supplied under contract at least, [subparagraphs "d" and "e" of clause 16](#) of this Annex of the irradiation process specification should form part of that contract.

#### V. COMMISSIONING OF THE PLANT

##### General

18. (12) Commissioning is the exercise of obtaining and documenting evidence that the irradiation plant will perform consistently within predetermined limits when operated according to the process specification. In

accordance with this Annex, predetermined limits are the maximum and minimum doses designed to be absorbed by the irradiation container. It must not be possible for variations to occur in the operation of the plant which give a dose to the container outside these limits without the knowledge of the operator.

19. (13) Commissioning should include the following elements:

- a) (a) design;
- б) (b) dose mapping;
- в) (c) documentation;
- г) (d) requirements for recommissioning of the unit.

#### Sources of gamma radiation

##### Design

20. (14) The absorbed dose received by a particular part of an irradiation container at any specific point around the irradiator depends, in particular, on the following factors:

- a) (a) activity and geometry of the radiation source;
- б) (b) distance from source to container;
- в) (c) the duration of irradiation, controlled by the timer setting or conveyor speed;
- г) (d) the composition and density of material, including other products, between the source and the particular part of the container.

21. (15) The total absorbed dose will in addition depend on the path of containers through a continuous irradiator or the loading pattern in a batch irradiator, and on the number of exposure cycles.

22. (16) For a continuous irradiator with a fixed path or a batch irradiator with a fixed loading pattern, and with a given source strength and type of product, the key plant parameter controlled by the operator is conveyor speed or timer setting.

##### Dose Mapping

23. (17) For the dose mapping procedure, the irradiator should be filled with irradiation container spacked with dummy products or a representative product of uniform density. Dosimeters should be placed throughout a minimum of three loaded irradiation containers which are passed through the irradiator, surrounded by similar containers or dummy products. If the product is not uniformly packed, dosimeters should be placed in a larger number of containers.

24. (18) The positioning of dosimeters will depend on the size of the irradiation container. For example, for containers up to 1 x 1 x 0.5 m, a three-dimensional 20 cm grid throughout the container including the outside surfaces might be suitable. If the expected positions of the minimum and maximum dose are known from a previous irradiator performance characterisation, some dosimeters could be removed from regions of average dose and replaced to form a 10 cm grid in the regions of extreme dose.

25. (19) The results of this procedure will give minimum and maximum absorbed doses in the product and on the container surface for a given set of plant parameters, product density and loading pattern.

26. (20) Ideally, reference dosimeters should be used for the dose mapping exercise because of their greater precision. Routine dosimeters are permissible but it is advisable to place reference dosimeters beside them at the expected positions of minimum and maximum dose and at the routine monitoring position in each of the replicate irradiation containers. The observed values of dose will have an associated random uncertainty which can be

estimated from the variations in replicate measurements.

27. (21) The minimum observed dose, as measured by the routine dosimeters, necessary to ensure that all irradiation containers receive the minimum required dose will be set in the knowledge of the random variability of the routine dosimeters used.

28. (22) Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.

#### Electron beam irradiators

##### Design

29. (23) The absorbed dose received by a particular portion of an irradiated product depends on the following factors:

a) (a) the characteristics of the beam, which are: electron energy, average beam current, scan width and scan uniformity;

б) (b) the conveyor speed;

в) (c) the product composition and density;

г) (d) composition, density and thickness of material between the output window and the particular portion of product;

д) (e) the output window to container distance.

30. (24) Key parameters controlled by the operator are the characteristics of the beam and the conveyor speed.

##### Dose Mapping

31. (25) For the dose mapping procedure, dosimeters should be placed between layers of homogeneous absorber sheets making up a dummy product, or between layers of representative products of uniform density, such that at least ten measurements can be made within the maximum range of the electrons. It is also necessary to comply with the requirements set out [items 24 - 27](#) of this Annex.

32. (26) Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.

##### Re-commissioning

33. (27) Commissioning should be repeated if there is a change to the process or the irradiator which could affect the dose distribution to the irradiation container (e.g. change of source pencils). The extent to re-commissioning depends on the extent of the change in their radiator or the load that has taken place. If in doubt, re-commission.

#### VI. PREMISES

34. (28) Premises should be designed and operated to segregate irradiated from non-irradiated containers to avoid their cross-contamination. Where materials are handled within closed irradiation containers, it may not be necessary to segregate pharmaceutical from non pharmaceutical materials, provided there is no risk of the former being contaminated by the latter.

Any possibility of contamination of the products by radionuclide from the source must be excluded.

#### VII. PROCESSING

36. (29) Irradiation containers should be packed in accordance with the specified loading pattern(s) established during validation.

37. (30) During the process, the radiation dose to the irradiation containers should be monitored using validated dosimetry procedures. The relationship between this dose and the dose absorbed by the product inside the container must have been established during process validation and plant commissioning.

38. (31) Radiation indicators should be used as an aid to differentiating irradiated from non-irradiated containers. They should not be used as the sole means of differentiation or as an indication of satisfactory processing.

39. (32) Processing of mixed loads of containers within the irradiation cell should only be done when it is known from commissioning trials or other evidence that the radiation dose received by individual containers remains within the limits specified.

40. (33) When the required radiation dose is by design given during more than one exposure or passage through the plant, this should be with the agreement of the holder of the marketing authorisation. and occur within a predetermined time period. Unplanned interruptions during irradiation should be notified to the holder of the marketing authorisation if this extends the irradiation process beyond a previously agreed period.

41. (34) Non-irradiated products must be segregated from irradiated products at all times. Methods of doing this include the use of radiation indicators ([item 38](#) of this Annex), and appropriate design of premises ([item 34](#) of this Annex).

#### Gamma irradiator

42. (35) For continuous processing modes, dosimeters should be placed so that at least two are exposed in the irradiation at all times.

43. (36) For batch mode, at least two dosimeters should be exposed in positions related to the minimum dose position.

44. (37) For continuous process mode, there should be a positive indication of the correct position of the source and an interlock between source position and conveyor movement. Conveyor speed should be monitored continuously and recorded.

45. (38) For batch process modes source movement and exposure times for each batch should be monitored and recorded.

46. (39) For a given desired dose, the timer setting or conveyor speed requires adjustment for source decay and source additions. The period of validity of the setting or speed should be recorded and adhered to.

#### Electron beam irradiators

47. (40) A dosimeter should be placed on every container.

48. (41) There should be continuous recording of average beam current, electron energy, scan-width and conveyor speed. These variables, other than conveyor speed, need to be controlled within the defined limits established during commissioning since they are liable to instantaneous change.

### VIII. DOCUMENTATION

49. (42) The numbers of containers received, irradiated and dispatched should be reconciled with each other and with the associated documentation. Any discrepancy should be reported and resolved.

50. (43) The irradiation plant operator should certify in writing the range of doses received by each irradiated container within a batch or delivery.

51. (44) Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and retained. The method and place of retention should be agreed between the plant operator and the holder of the marketing authorisation.

52. (45) The documentation associated with the validation and commissioning of the plant should be retained for one year after the expiry date or at least five years after the release of the last product processed by the plant, whichever is the longer.

## IX. MICROBIOLOGICAL MONITORING

53. (46) Microbiological monitoring is the responsibility of the pharmaceutical manufacturer. It may include environmental monitoring where product is manufactured and pre-irradiation monitoring of the product as specified in the marketing authorisation.

Annex No. 13  
to Good Manufacturing  
Practice

## INVESTIGATIONAL MEDICINAL PRODUCTS

### I. PRINCIPLE

1. Investigational medicinal products should be produced in accordance with this [Practice](#) and Provisions of relevant regulatory legal acts of the Russian Federation where relevant and as appropriate to the stage of development of the product. Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.

2. In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products.

3. The application of the [GMP](#) to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture.

4. Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified.

5. The production of investigational medicinal products involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, and the need for randomisation and coding (blinding) and increased risk of product cross-contamination and mix up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation, or, marketed products may be used which have been re-packaged or modified in some way. The manufacturer's personnel should undergo the training in the application of the [GMP](#) to investigational medicinal products. Co-operation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products. The increased complexity in manufacturing operations requires a highly effective pharmaceutical quality system.

6. The Annex also includes guidance on ordering, shipping, and returning clinical supplies.

#### Non-investigational medicinal products

7. Products other than the test product, placebo or comparator may be supplied to subjects participating in a



trial. Such medicinal products may be used as support or escape medication for preventative, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the trial protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator. The sponsor should ensure that they are in accordance with the notification/ request for authorisation to conduct the trial and that they are of appropriate quality for the purposes of the trial, Taking into account the source of the materials, whether or not they are the subject of a marketing authorisation and whether they have been repackaged. The advice and involvement of a qualified person is recommended in this task.

#### Manufacturing authorisation and reconstitution

8. Both the total and partial manufacture of investigational medicinal products, as well as the various processes of dividing up, packaging or presentation, is subject to the authorisation. This authorisation shall not be required for reconstitution of products in healthcare organizations.

9. For the purpose of this provision, reconstitution shall be understood as a simple process of:

dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject, or

diluting or mixing the investigational medicinal product(s) with some other substance(s) used as a vehicle for the purposes of administering it.

10. Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product.

11. An investigational medicinal product must exist before a process can be defined as reconstitution.

12. The process of reconstitution has to be undertaken as soon as practicable before administration.

13. This process has to be defined in the clinical trial application / IMP dossier and clinical trial protocol, or related document, available in healthcare organization.

## II. TERMS AND DEFINITIONS

14. In the context of this Annex, the following basic concepts are used:

Product Specification File (IMP dossier) is a set of documents containing all the information (or referring to relevant documents) necessary to draft the detailed written instructions on processing, packaging, quality control, batch release and shipping of an investigational medicinal product;

order - instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).

IMP importer - a person who has the right to import the investigational medicinal products, drawn up in accordance with the regulatory legal acts of the Russian Federation;

Investigator - A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigational medicinal product - a medicinal product or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Clinical trial - any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an

investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the object of ascertaining its/their safety and/or efficacy.

Shipping - the operation of packaging for shipment and sending of ordered medicinal products for clinical trials.

Comparator product - an investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Randomisation Code - a listing in which the treatment assigned to each subject from the randomisation process is identified.

Randomisation - the process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Blinding - a procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.

Sponsor - a legal entity which takes responsibility for organization of a clinical trial.

### III. QUALITY MANAGEMENT

15. (1) The pharmaceutical quality system, designed and verified by the manufacturer, should comply with the requirements of this [Practice](#), applicable to investigational medicinal products. It should also be described in written procedures available to the sponsor.

16. (2) The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained.

### IV. PERSONNEL

17. (3) All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.

18. Even in cases where the number of staff involved is small, there should be, for each batch, separate people responsible for production and quality control.

19. (4) The Qualified Person should ensure that there are systems in place that meet the requirements of the Annex. The qualified person should have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Qualified Person in connection with the assessment of investigational medicinal products is given in [items 61 - 65](#) of this Annex.

### V. PREMISES AND EQUIPMENT

20. (5) The toxicity, potency and sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection / test methods and acceptance limits to be used after cleaning should reflect the nature of these risks. Consideration should be given to campaign working where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

### VI. DOCUMENTATION

Specifications and instructions

21. (6) Specifications (for starting materials, primary packaging materials, intermediate, bulk products and finished products), manufacturing formulae and processing and packaging instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, requirements of the State Pharmacopoeia of the Russian Federation and regulatory legal acts of the Russian Federation, New version should allow traceability to the previous document. Any changes should be carried out according to a written procedure, which should address any implications for product quality such as stability and bio equivalence.

22. (7) Rationales for changes should be recorded and documented. The consequences of a change on product quality and on any on-going clinical trials should be investigated. The results of such investigation should be documented.

#### Order

23. (8) The order should request the processing and/or packaging of a certain number of units and/or their shipping. The order should be given by or on behalf of the sponsor to the manufacturer. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorised and refer to the Product Specification File (IMP dossier) and the relevant clinical trial protocol as appropriate.

#### IMP dossier (or Product Specification File)

24. (9) Product Specification File (IMP dossier) should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions.

25. It should include, or refer to, the following documents:

Specifications and analytical methods for starting materials, packaging materials;

Intermediate, bulk and finished product;

Manufacturing methods;

In-process testing and methods;

Approved label copy;

Relevant clinical trial protocols and randomisation codes, as appropriate;

Relevant technical agreements with contract givers, specified in [paragraphs 237 - 255](#) of the Practice, as appropriate;

Stability data;

Storage and shipment conditions.

26. The above listing is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development. The information should form the basis for assessment of the suitability for certification and release of a particular batch by the qualified person and should therefore be accessible to him/her. Where different manufacturing steps are carried out at different locations under the responsibility of different Qualified Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

#### Manufacturing Formulae and Processing Instructions

27. (10) For every manufacturing operation or supply there should be clear and adequate written instructions and written records. Where an operation is not repetitive it may not be necessary to produce Master Formulae and

Processing Instructions. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorisation is granted.

28. (11) The information in the Product Specification File (IMP dossier) should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping.

#### Packaging Instructions

29. (12) Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and any retention samples to be kept. After packaging and labeling, sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.

#### Processing, testing and packaging batch records

30. (13) Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify the procedures used and any changes made, enhance knowledge of the product and develop the manufacturing operations.

31. (14) Batch manufacturing records should be retained at least five years after the completion or termination of the last clinical trial in which this batch was used.

### VII. MANUFACTURE

#### Packaging materials

32. (15) Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.

#### Manufacturing operations

33. (16) During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continually to the experience gained in production. Parameters identified and controlled should be justifiable based on knowledge available at the time.

34. (17) Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production. Anyway, premises and equipment are expected to be qualified For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing. Likewise, when required, virus inactivation/removal and that of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products, by following the scientific principles and techniques defined in the available guidance in this area.

35. (18) Validation of aseptic processes presents special problems when the batch size is small. In these cases the number of units filled may be the maximum number filled in production. If practicable, and otherwise consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained. Filling and sealing is often a manual or semi-automated operation presenting great challenges to sterility. So enhanced attention should be given to operator training, and validating the aseptic technique of individual operators.

#### Principles applicable to comparator product

36. (19) If a comparator product is modified, data should be available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.

37. (20) The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable use-by date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.

#### Blinding operations

38. (21) Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded" products when necessary, including the batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency.

#### Randomisation code

39. (22) Procedures should describe the generation, security, distribution, handling and retention of any randomisation code used for packaging investigational products, and code-break mechanisms. Appropriate records should be maintained.

#### Packaging operations

40. (23) During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product mixup must be minimised by using appropriate procedures and/or, specialised equipment as appropriate and relevant staff training.

41. (24) Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors (which are also harder to detect) than for marketed products. Particularly when "blinded" products with similar appearance are used. Precautions against mis-labelling such as label reconciliation, line clearance, in process control checks by appropriately trained staff should accordingly be intensified.

42. (25) The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

#### Labelling

43. (26) [Table 1](#) summarises the contents of items 43 - 48 of this Annex. Labelling should ensure the subject's protection, traceability and identification of the medicinal product and trial, as well as promote the correct use of investigational medicinal products.

44. The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system:

a) (a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);

b) (b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;

b) (c) batch and/or code number to identify the contents and packaging operation;

r) (d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

d) (e) the trial subject identification number/treatment number and where relevant, the visit number;

e) (f) the name and initials of the investigator (if not included in [subparagraphs "a" or "d"](#));

ж) (g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);

з) (h) "For clinical trial use only" wording;

и) (i) the storage conditions;

к) (j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.

л) (k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

45. (27) The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

46. (28) Particulars should appear in Russian language. The particulars listed in [item 44](#) of the Annex should appear on the primary and on the secondary packaging (except for the cases described in [items 47 - 48](#) of the Annex). The requirements with respect to the contents of the label on the primary and outer packaging are summarised in [Table 1](#). Other languages may be included.

47. (29) When the product is to be provided to the trial subject or the person administering the medication within a primary package together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in [item 44](#) of the Annex, the following information shall be included on the label of the primary package (or any sealed dosing device that contains the primary packaging):

a) (a) name of sponsor, contract research organisation or investigator;

б) (b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;

в) (c) batch and/or code number to identify the contents and packaging operation;

г) (d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

д) (e) the trial subject identification number/ treatment number and where relevant, the visit number.

48. (30) If the primary packaging takes the form of blister packs or small units such as ampoules on which the particulars required in [item 44](#) of the Annex), cannot be displayed, secondary packaging should be provided bearing a label with those particulars. The primary packaging should nevertheless contain the following:

a) (a) name of sponsor, contract research organisation or investigator;

б) (b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;

в) (c) batch and/or code number to identify the contents and packaging operation;

г) (d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

д) (e) the trial subject identification number/ treatment number and where relevant, the visit number.

Table 1. Label summarized information ([paragraphs 43 - 48](#))

name, address and telephone number  
of the sponsor, contract research

organisation or investigator (the main COMMON CASE contact for information For primary packaging on the product, secondary packaging (para. clinical trial and emergency 44) unblinding);

Information, |  
given in subparagraphs |  
"a" <1> - "д" |

#### PRIMARY PACKAGING

If the primary package together with secondary packaging is intended to remain together (para. 47) <5>

Information, |  
given in subparagraphs |

б) pharmaceutical dosage form, route of administration, | "a" <2> "б" <3> "в" "г" | quantity of dosage units, and in the case of | "д" | open label trials, - | the name/identifier and strength/potency;

в) batch and/or code number to identify the contents and packaging operation;

г) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

д) the trial subject identification number/treatment number and and where relevant, the visit number.

е) the name and initials of the investigator (if it is not included in subparagraphs "a" or "г");

ж) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);

з) "For clinical trial use only" or similar wording;

и) the storage conditions; PRIMARY PACKAGING

к) period of use expiry date), in month Blister packs or /year format to avoid any small units (para. 48)

ambiguity (period of use <5>

stated for the product | use-bydate, the expiry date or re-test date) may be indicated | Control | records); | given in subparagraphs |

л) "keep out of reach of children" writing | "a" <2> "б" <3>, <4> "в" | except when | "г" "д" |

the product is for use in trials | | where the product is not taken home by subjects. | |

#### Notes:

<1> The address and telephone number of the main contact for information on the product, clinical trial and

for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times ([item 45](#) of this Annex).

<2>The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not be included.

<3> Route of administration may be excluded for oral solid dose forms.

<4> The pharmaceutical dosage form and quantity of dosage units may be omitted.

<5> When the outer packaging carries the particulars listed in [item 44](#) of the Annex.

49. (31) Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

50. (32) For clinical trials when:

a) there is no need for divide production or packaging processes;

b) medicinal products marketed, produced or imported in accordance with the legislation of the Russian Federation are used for clinical trials;

c) only patients with those diseases that correspond to the indications for use approved at authorisation, can be trial subjects.

On the primary packaging, there should appear so as not to close the original label, the following particulars:

(i) name of the sponsor, contract research organisation or investigator;

(ii) a trial reference code allowing identification of the trial site, investigator and trial subject;

51. (33) If it is necessary to change use-by-date for a investigational medicinal product, the packaging needs bear an additional label. A new use-by-date and, repeatedly, batch number should appear on the additional label. The additional label can be glued over the old date of use, but it should not cover the original batch number that is required for quality control. The additional labeling should be carried out by organizations licensed to manufacture medicinal products or to perform pharmaceutical activities (storage of medicinal products for medical use). If necessary, there pharmaceutical worker of additional label may be carried out in a medical organization by a pharmaceutical worker of this organization or under his supervision, or by a medical worker of a medical organization in accordance with the requirements of the legislation of the Russian Federation. If this is not possible, additional labelling may be carried out by a clinical trial monitor that has undergone an adequate training. The activity in question should be carried out in accordance with this [Practice](#), special and standard operating procedures, and, if necessary, transfer them to another organization under the contract. The operation must be supervised by another employee. The activity should be adequately and carefully documented both in clinical trial documents and batch records.

## VIII. QUALITY CONTROL

52. (34) As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets its specification.

53. (35) Quality control should be performed in accordance with the Product Specification File (IMP dossier). Verification of the effectiveness of blinding should be performed and recorded.

54. (36) Samples are retained to fulfill two purposes: firstly to provide a sample for analytical testing and secondly to provide a specimen of the finished product. Samples may therefore fall into two categories:

Reference sample: a sample of a batch of starting material, packaging material, product contained in its primary packaging or finished product which is stored for the purpose of being analysed should the need arise. Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing



and release) or intermediates, which are transported outside of the manufacturer's control, should be kept.

Retention sample: a sample of a packaged unit from a batch of finished product It is stored for identification purposes. For example, presentation, packaging, labeling, leaflet, batch number, expiry date should the need arise.

55. In many instances the reference and retention samples will be presented identically, i.e.as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable. Reference and retention samples of investigational medicinal product, including blinded product should be kept for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.

56. Consideration should be given to keeping retention samples until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.

57. (37) The storage location of Reference and Retention samples should be defined in a Technical Agreement between the sponsor and manufacturer(s). These locations should allow timely access by representatives of the authorized federal executive body.

58. Reference samples of finished product should be stored within the Russian Federation or in a third country where appropriate arrangements have been made by the Russian Federation with the exporting country to ensure that the manufacturer of the investigational medicinal product applies standards of good manufacturing practice at least equivalent to those of the [Practice](#) laid down by Russia. In exceptional circumstances the reference samples of the finished product may be stored by the manufacturer in another third country, In which case this should be justified, and documented in a technical agreement between the sponsor, importer in the Russian Federation and that third country manufacturer.

59. The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the IMP dossier submitted for authorisation to conduct the clinical trial to the authorized federal executive body.

60. In the case of retention samples, it is acceptable to store information related to the final packaging as written or electronic records if such records provide sufficient information. In the case of the latter, the system should comply with the requirements of [Annex No. 11](#) to this GMP.

## IX. RELEASE OF BATCHES

61. (38) Release of investigational medicinal products should not occur until after the Qualified Person has certified that the established requirements have been met taking into account [items 62 - 63](#) of the Annex.

62. (39) The duties of the Qualified Person in relation to investigational medicinal products are affected by the different circumstances that can arise and are referred to below:

a) Product manufactured within the Russian Federation but not subject to an Russian Federation marketing authorisation: when applying for a permit to conduct a clinical trial, it must be ascertained that the investigational medicinal product is manufactured and tested in accordance with the requirements of this [Practice](#), Product Specification File (IMP dossier), as well as there is a relevant information, provided by the sponsor to the authorized federal executive body;

b) the medicinal product is marketed in the Russian Federation, supplied by a wholesale organization located in the Russian Federation, regardless of where the medicinal product is manufactured: the duties are as described above, in [subparagraph "a"](#), the scope of certification can be limited to assuring that the products are in accordance with the request for authorisation to conduct the trial and any subsequent processing for the purpose of blinding, trial-specific packaging and labelling. The Product Specification File (IMP dossier) will be similarly restricted in scope ([items 24 - 26](#) of the Annex);

b) the product imported directly from a 3rd country: when applying for a permit to conduct a clinical trial, it must be ascertained that the investigational medicinal product is manufactured and tested in accordance with the guidelines of Good Manufacturing Practice provided that their standards at least equivalent to [Practice](#), Product

Specification File, as well as there is a relevant information, provided by the sponsor to the authorized federal executive body. Where investigational medicinal products are imported from a 3rd country and they are subject to arrangement concluded between the Russian Federation and that country, such as a Mutual Recognition Agreement (MRA), equivalent to standards of [Practice](#) (Good Manufacturing Practice) apply provided any such agreement is relevant to the product in question. In the absence of an MRA, the Qualified Person should determine that equivalent standards of this [GMP](#) apply through knowledge of the quality system employed at the manufacturer. This knowledge is normally acquired through audit of the manufacturer's quality system. In either case, the Qualified Person may then certify on the basis of documentation supplied by the 3rd country manufacturer (see [item 63](#) of this Annex);

r) For imported comparator products where adequate assurance cannot be obtained in order to certify that each batch has been manufactured to equivalent standards of this [GMP](#), the duty of the Qualified Person is to confirm that each series produced has passed all the kinds of controls and tests necessary to confirm its quality, and that there is relevant information provided by the sponsor to the authorized federal executive body.

63. (40) Assessment of each batch for certification prior to release may include as appropriate:

batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomisation code. These records should include all deviations or planned changes, and any consequent additional checks or tests, And should be completed and endorsed by the staff authorised to do so according to the quality system;

production conditions;

the validation status of facilities, processes and methods;

examination of finished packs;

where relevant, the results of any analyses or tests performed after importation;

stability reports;

the source and verification of conditions of storage and shipment;

audit reports concerning the quality system of the manufacturer;

documents certifying that the manufacturer is authorised to manufacture investigational medicinal products or comparators for export by the appropriate authorized federal executive body;

where relevant, the Russian Federation regulatory requirements for marketing authorisation, this [GMP](#) standards applicable and any official verification of [GMP](#) compliance from the authorized federal executive body;

all other factors of which the QP is aware that are relevant to the quality of the batch.

64. The relevance of the above elements is affected by the country of origin of the product, the manufacturer, and the marketed status of the product (with or without a marketing authorisation, in the Russian Federation or in a third country) and its phase of development. The sponsor should ensure that the elements taken into account by the qualified person when certifying the batch are consistent with the information provided by the authorized federal executive body when submitting the clinical trial application, see ([para. 68](#) of this Practice).

65. (41) Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Qualified Persons, the recommendations listed in [Annex No. 16](#) to the GMP should be followed as applicable.

66. (42) Where, permitted in accordance with this [Practice](#), and other regulatory legal acts of the Russian Federation, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the Qualified Person is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of this [Practice](#) and should seek the

advice of the Qualified Person in this regard.

#### X. SHIPPING

67. (43) Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step procedure: certification by the Qualified Person; and release by the sponsor for use in a clinical trial following fulfillment of the established requirements. Both steps should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.

68. (44) Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.

69. (45) De-coding arrangements should be available to the appropriate responsible personnel before investigational medicinal products are shipped to the investigator site.

70. (46) A detailed inventory of the shipments made by the manufacturer or importer should be maintained. It should particularly mention the addressees' identification.

71. (47) Transfers of investigational medicinal products from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer, through for example, trial monitoring reports and records of storage conditions at the original trial site should be reviewed, as part of the assessment of the product's suitability for transfer. And the advice of the Qualified person should be sought. The product should be returned to the manufacturer, for re-labelling, if necessary, and certification by a Qualified Person. Records should be retained and full traceability ensured.

#### XI. COMPLAINTS

72. (48) The conclusions of any investigation carried out in relation to a complaint which could arise from the quality of the product should be discussed between the manufacturer or importer and the sponsor (if different). This should involve the Qualified Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

#### XII. RECALLS AND RETURNS

##### Recalls

73. (49) Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator and monitor need to understand their obligations under the retrieval procedure.

74. (50) The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.

##### Returns

75. (51) Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.

76. (52) Returned investigational medicinal products should be clearly identified. They should be stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.

#### XIII. DESTRUCTION

77. (53) The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorisation by the Sponsor.

78. (54) The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor.

79. (55) When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

Annex No. 14  
to Good Manufacturing  
Practice

## MANUFACTURE OF MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD OR PLASMA

### I. TERMS AND DEFINITIONS

1. The following basic concepts are used for the purpose of this Annex:

Blood component means a therapeutic constituent of blood (red cells, white cells, platelets and plasma) that can be prepared by various methods;

Blood means whole blood collected from a donor and processed either for transfusion or for further manufacturing.

Medicinal products derived from human blood or human plasma are medicinal products based on blood constituents which are prepared industrially;

Processing means any step in the preparation of blood component that is carried out between the collection of blood and the issuing of a blood component, e.g. separation and freezing of blood components. In this Annex, processing in addition refers to those operations performed at the blood establishment that are specific to plasma to be used for fractionation.

Plasma Master File (PMF) is a stand-alone document, which is separate from the dossier for marketing authorisation. It provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipients and active substances, which are part of plasma, derived medicinal products or medical devices.

Responsible Person (RP) is a specially appointed person in the blood collection and testing establishments that is responsible for:

for ensuring that any aspect of the collection and testing of human blood and blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion are conducted in accordance with the legislation of the Russian Federation.

providing the authorized federal executive bodies with the necessary information regarding regulations, permits, accreditation or licensing;

complying with the requirements of the legislation of the Russian Federation in the establishment relating to blood collection and testing.

The responsible person must meet the following qualification conditions:

have a higher medical or biological education;

have at least two years of work experience in one or more establishments for collection and testing of human blood that perform the collection and testing of human blood and blood components, or their preparation, storage and distribution.

The above responsibilities of the responsible person can be transferred to other persons who have the appropriate qualifications and work experience to fulfill these responsibilities.

Blood establishments should notify the authorized federal executive body of the name, first name and patronymic (if any) of the responsible person, as well as the persons to whom the duties have been transferred, specifying the range of duties assigned to them.

If the responsible person or persons to whom the duties of the responsible person have been transferred are replaced on a permanent basis or ad interim, blood establishment should immediately notify the authorized federal executive body of the surname, first name and patronymic (if any) of the new person in charge and date his appointment;

Plasma for fractionation is the liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration or centrifugation of anti-coagulated blood in an apheresis procedure. It is intended for the manufacture of plasma derived medicinal products, described in the State Pharmacopoeia of the Russian Federation, in particular albumin, coagulation factors and immunoglobulins of human origin;

Blood products mean any therapeutic product derived from human blood or plasma;

Third countries contract fractionation program is a contract fractionation in a plant of a fractionator/manufacturer in the Russian Federation using starting material from third countries and manufacturing products not intended for the Russian market;

Blood establishment is any legal entity that is responsible for any aspect of the collection and testing of human blood and blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion. While this definition does not include hospital blood banks, it is understood to include centres where apheresis of plasma is performed;

Fractionation, fractionation plant. Fractionation is the manufacturing process in a plant (fractionation plant) during which plasma components are separated/purified by various physical and chemical methods such as e.g. precipitation, chromatography.

## II. SCOPE (1)

2. (1.1) The provisions of this Annex apply to medicinal products derived from human blood or plasma, fractionated in or imported into the Russian Federation. The Annex applies also to the starting material (e.g. human plasma) for these products. The requirements apply also for stable derivatives of human blood or human plasma (e.g. Albumin) incorporated into medical devices.

3. (1.2) This Annex defines specific requirements for processing, storage and transport of human plasma used for fractionation and for the manufacture of medicinal products derived from human blood or plasma.

4. (1.3) The Annex addresses specific provisions for when starting material is imported from third countries and for contract fractionation programs for third countries.

5. (1.4) The Annex does not apply to blood components intended for transfusion.

## III. PRINCIPLES (2)

6. (2.1) Medicinal products derived from human blood or plasma (and their active substances which are used as starting materials) must comply with the principles and guidelines of this [GMP](#), as well as the relevant marketing authorisation. They are considered to be biological medicinal products and the starting materials include biological substances, such as cells or fluids (including blood or plasma) of human origin. Certain special features arise from the biological nature of the source material. For example, disease transmitting agents, especially viruses, may contaminate the source material. The quality and safety of these products relies therefore on the control of source materials and their origin as well as on the subsequent manufacturing procedures, including infectious marker testing, virus removal and virus inactivation.

7. (2.2) All active substances used as starting material for medicinal products must comply with the principles and guidelines of this [Practice](#) (see item 6 of this Annex). For starting materials derived from human blood and plasma the requirements for the collection and testing are to be followed. Collection and testing must be performed in accordance with an appropriate quality system, the provisions of appropriate regulatory legal acts of the Russian Federation and the relevant specifications. Furthermore, the requirements of the regulatory legal acts of the Russian Federation on traceability and serious adverse reactions and serious adverse event notifications from the donor to the recipient apply. In addition, the monographs of the State Pharmacopoeia of the Russian Federation are to be observed.

8. (2.3) Starting material for the manufacture of medicinal products derived from human blood or plasma imported from third countries and intended for use or distribution in the Russian Federation must meet standards which are equivalent to RF standards relating to a quality system for blood establishments; As well as the requirements of traceability and serious adverse reaction and serious adverse event notification from the donor to the recipient as set out in the regulatory legal acts of the Russian Federation and the technical requirements for blood and blood components as set out in the regulatory legal acts of the Russian Federation.

9. (2.4) In the case of third country contract fractionation programs the starting material imported from third countries must be in compliance with the quality and safety requirements as laid down in the regulatory legal acts of the Russian Federation. The activities conducted within the Russian Federation must fully comply with this [GMP](#). Consideration should be given to the RF standards and specifications relating to a quality system for blood establishments, as well as the traceability requirements, notification of serious adverse reactions and events, and technical requirements for blood and blood components set out in the regulatory legal acts of the Russian Federation.

10. (2.5) For all subsequent steps after collection and testing (e.g. processing (including separation), freezing, storage and transport to the manufacturer) the requirements of this [GMP](#) apply. Normally, these activities would be carried out under the responsibility of a Qualified Person of the manufacturer. Where specific processing steps in relation to plasma for fractionation take place in a blood establishment, the specific appointment of a Qualified Person may, however, not be proportionate given the presence and responsibility of a Responsible Person. To address this particular situation and to ensure the legal responsibilities of the Qualified Person set out in the regulatory legal acts of the Russian Federation are properly addressed, the fractionation plant/manufacturer should establish a contract in accordance with [paragraphs 237 - 255](#) of the GMP with the blood establishment. The contract defines respective responsibilities and the detailed requirements in order to ensure compliance. The Responsible Person of the blood establishment and the Qualified Person of the fractionation/manufacturing plant should be involved in drawing up this contract. The Qualified Person should ensure that audits are performed to confirm that the blood establishment complies with the contract.

11. (2.6) Specific requirements for documentation and other arrangements relating to the starting material of plasma-derived medicinal products are defined in the Plasma Master File.

#### IV. QUALITY MANAGEMENT (3)

12. (3.1) Quality management should govern all stages from donor selection to delivery of the finished product. Reference is made to the regulatory legal acts of the Russian Federation for traceability up to and including the delivery of plasma to the fractionation plant, and for all stages concerning collection and testing of human blood and human plasma to be used for the manufacture of medicinal products.

13. (3.2) Blood or plasma used as source material for the manufacture of medicinal products must be

collected by blood establishments and be tested in laboratories which apply quality systems in accordance with the requirements of the regulatory legal acts of the Russian Federation, are authorised by a competent federal executive body and are subject to regular inspections as referred to the legislation of the Russian Federation. Third country contract fractionation programs have to be notified to the competent federal executive body.

14. (3.3) If plasma is imported from third countries it should only be purchased from approved suppliers (e.g. blood establishments, including external warehouses). They should be named in the specifications for starting materials as defined by the fractionation plant/manufacturer, and be accepted by an competent federal executive authority in cases and in the manner provided for by regulatory legal acts of the Russian Federation, and by the Qualified Person of the fractionation plant in the Russian Federation. Certification and release of plasma (plasma for fractionation) as starting material is mentioned in [item 39](#) of the Annex.

15. (3.4) Supplier qualification, including audits, should be performed by the fractionation plant/manufacturer of the finished product according to written procedures. Re-qualification of suppliers should be performed at regular intervals taking a risk-based approach into account.

16. (3.5) The fractionation plant/manufacturer of the finished product should establish written contracts with the supplying blood establishments.

17. As a minimum the following key aspects should be addressed:

definition of duties and respective responsibilities;

quality system and documentation requirements;

donor selection criteria and testing;

requirements for the separation of blood into blood components/plasma;

freezing of plasma;

storage and transport of plasma;

traceability and post donation / collection information (including adverse events).

18. The test results of all units supplied by the blood establishment should be available to the fractionation plant/manufacturer of the medicinal product. In addition, any fractionation step subcontracted should be defined in a written contract.

19. (3.6) A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality or safety of the products, or traceability. The potential impact of proposed changes should be evaluated. The need for additional testing and validation, especially viral inactivation and removal steps, should be determined.

20. (3.7) An adequate safety strategy should be in place to minimise the risk from infectious agents and emerging infectious agents. This strategy should involve a risk assessment that:

defines an inventory holding time (internal quarantine time) before processing the plasma, i.e. to remove look back units (units previously collected within a particular time frame determined in the regulatory legal acts of the Russian Federation, before it is determined that they are from "high risk" donors should be excluded from processing, for example, if confirmatory testing is positive);

considers all aspects of virus reduction and/or testing for infectious agents or surrogates;

considers the virus reduction capabilities, the pool size and other relevant aspects of the manufacturing processes.

## V. TRACEABILITY AND POST COLLECTION MEASURES

(4)

21. (4.1) There must be a system in place that enables each donation to be traced, from the donor and the donation via the blood establishment through to the batch of medicinal product and vice versa.

22. (4.2) Responsibilities for traceability of the product should be defined (there should be no gaps);

from the donor and the donation in the blood establishment to the fractionation plant (this is the responsibility of the RP at the blood establishment),

from the fractionation plant to the manufacturer of the medicinal product and any secondary facility, whether a manufacturer of a medicinal product or of a medical device (this is the responsibility of the QP).

23. (4.3) Data needed for full traceability must be stored for at least 30 years unless otherwise provided by the legislation of the Russian Federation.

24. (4.4) The contracts, as mentioned in [item 16](#) of the Annex, between the blood establishments (including testing laboratories) and the fractionation plant/manufacturer should ensure that traceability and post collection measures cover the complete chain from the collection of the plasma to all manufacturers responsible for release of the final products.

25. (4.5) The blood establishments should notify the fractionating plant/manufacturer of any event which may affect the quality or safety of the product, and other relevant information found subsequent to donor acceptance or release of the plasma, e.g. look back information (post-collection information) Where the fractionation plant/manufacturer is located in a third country, the information should be forwarded to the manufacturer in RF responsible for release of any product manufactured from the plasma concerned. In both cases, if relevant for the quality or safety of the final product, this information should be forwarded to the competent federal executive body responsible for the fractionation plant/manufacturer.

26. (4.6) The notification procedure as described in [item 25](#) of the Annex also applies when an inspection of a blood establishment by a competent federal executive authority leads to a withdrawal of an existing licence/certificate.

27. (4.7) The management of post-collection information should be described in standard operating procedures and taking into account obligations and procedures for informing the competent authorities. Post-collection measures should be available as defined in the regulatory legal acts of the Russian Federation.

## VI. PREMISES AND EQUIPMENT (5)

28. (5.1) In order to minimise microbiological contamination or the introduction of foreign material into the plasma pool, thawing and pooling of plasma units should be performed in an area conforming to at least to the Grade D requirements defined in [Annex No 1](#) to this GMP. Appropriate clothing should be worn including face masks and gloves. All other open manipulations during the manufacturing process should be done under conditions conforming to the appropriate requirements of [Annex No 1](#) to the GMP.

29. (5.2) Environmental monitoring should be performed regularly, especially during the 'opening' of plasma containers, and during subsequent thawing and pooling processes in accordance with [Annex No 1](#) of the GMP. Acceptance limits should be specified.

30. (5.3) In the production of plasma-derived medicinal products, appropriate viral inactivation or removal procedures are used and steps should be taken to prevent cross contamination of treated with untreated products. Dedicated and distinct premises and equipment should be used for manufacturing steps after viral inactivation treatment.

31. (5.4) To avoid placing routine manufacture at risk of contamination from viruses used during validation studies, the validation of methods for virus reduction should not be conducted in production facilities. Validation should be performed according to the requirements set out in the appropriate regulatory legal acts of the Russian Federation.



## VII. MANUFACTURING (6)

### Starting materials

32. (6.1) The starting material should comply with the requirements of all relevant monographs of the State Pharmacopoeia of the Russian Federation and of the conditions laid down in the respective marketing authorisation dossier including the Plasma Master File. These requirements should be defined in the written contract ([item 16](#) of this Annex) between the blood establishment and the fractionating plant/ manufacturer; And controlled through the quality system.

33. (6.2) Starting material for third country contract fractionation programs should comply with the requirements as specified in [item 9](#) of this Annex.

34. (6.3) Depending on the type of collection (i.e. either whole blood collection or automated apheresis) different processing steps may be required. All processing steps (e.g. centrifugation and/or separation, sampling, labelling, freezing) should be defined in written procedures.

35. (6.4) Any mix-ups of units and of samples, especially during labelling, as well as any contamination, e.g. when cutting the tube segments/sealing the containers, must be avoided.

36. (6.5) Freezing is a critical step for the recovery of proteins that are labile in plasma, e.g. clotting factors. Freezing should therefore be performed as soon as possible after collection, following a validated method. Therefore, the process requires observance of the monographs of State Pharmacopoeia of the Russian Federation.

37. (6.6) The storage and transport of blood or plasma at any stage in the transport chain to the fractionation plant should be defined and recorded Any deviation from the defined temperature should be notified to the fractionation plant. Qualified equipment and validated procedures should be used.

### Certification/release of plasma for fractionation as starting material

38. (6.7) Plasma for fractionation should only be released, i.e. from a quarantine status, through systems and procedures that assure the quality needed for the manufacture of the finished product. It should only be distributed to the plasma fractionation plant/manufacturer after it has been documented by the Responsible Person (or in case of blood/plasma collection in third countries by a person with equivalent responsibilities and qualifications) that the plasma for fractionation does comply with the requirements and specifications defined in the respective written contracts and that all steps have been performed in accordance with this [Practice](#).

39. (6.8) On entering the fractionation plant, the plasma units should be released for fractionation under the responsibility of the Qualified Person. The Qualified Person should confirm that the plasma complies with the requirements of all relevant monographs of the State Pharmacopoeia of the Russian Federation and the conditions laid down in the respective marketing authorisation dossier, including the Plasma Master File or, in case of plasma to be used for third country contract fractionation programs, with the requirements as specified in [item 9](#) of this Annex.

### Processing of plasma for fractionation

40. (6.9) The steps used in the fractionation process vary according to product and manufacturer. Usually, they include several fractionation/ purification procedures, some of which may contribute to the inactivation and/or removal of potential contamination.

41. (6.10) Requirements for the processes of pooling, pool sampling and fractionation/purification and virus inactivation/removal should be defined and followed thoroughly.

42. (6.11) The methods used in the viral inactivation process should be undertaken with strict adherence to validated procedures; And in compliance with the methods used in the virus validation studies. Detailed investigation of failures in virus inactivation procedures should be performed. Adherence to the validated production process is especially important in the virus reduction procedures as any deviation could result in a safety risk for

the final product. Procedures should be in place, that take this risk into consideration.

43. (6.12) Any reprocessing or reworking may only be performed after a quality risk management exercise has been performed and using processing steps as defined in the relevant Manufacturing Formulae.

44. (6.13) A system for clearly segregating/ distinguishing between products or intermediates which have undergone a process of virus reduction, from those which have not, should be in place.

45. (6.14) Depending on the outcome of a thorough risk management process (taking into consideration possible differences in epidemiology) production in campaigns including clear segregation and defined validated cleaning procedures should be adopted when plasma/intermediates of different origins is processed at the same plant. The requirement for such measures should be based on the appropriate regulatory legal act of the Russian Federation. The risk management process should consider whether it is necessary to use dedicated equipment in the case of third country contract fractionation programs.

46. (6.15) For intermediate products intended to be stored, a shelf-life should be defined based on stability data.

47. (6.16) The storage and transport of intermediate and finished medicinal products at any stage of the transport chain should be specified and recorded. Qualified equipment and validated procedures should be used.

#### VIII. QUALITY CONTROL (7)

48. (7.1) Testing requirements for viruses or other infectious agents should be considered in the light of knowledge emerging on infectious agents and on the availability of validated test methods.

49. (7.2) The first homogeneous plasma pool (e.g. after separation of the cryoprecipitate from the plasma pool) should be tested using validated test methods of suitable sensitivity and specificity, according to the relevant monographs of the State Pharmacopoeia of the Russian Federation.

#### IX. RELEASE OF INTERMEDIATE AND FINISHED PRODUCTS (8)

50. (8.1) Only batches derived from plasma pools tested and found negative for virus markers and found in compliance with the relevant monographs of the State Pharmacopoeia of the Russian Federation, including any specific virus cut-off limits, and with the approved specifications (e.g. Plasma Master File), should be released.

51. (8.2) The release of intermediates intended for further in-house processing or delivery to a different site, and, the release of finished products should be performed by the Qualified Person and in accordance with the established requirements.

52. (8.3) The release of intermediates and final products used in third country contract fractionation programs should be performed by the Qualified Person on the basis of standards agreed with the contract giver, and compliance with the standards of the [Practice](#). Compliance with relevant RF State Pharmacopoeia monographs may not be applicable, as these products are not intended for the use on the Russian market.

#### X. RETENTION OF PLASMA POOL SAMPLES (9)

53. (9.1) One plasma pool may be used to manufacture more than one batch and/or product. Retention samples and corresponding records from every pool should be kept for at least one year after the expiry date of the finished medicinal product with the longest shelf-life derived from the pool.

#### XI. DISPOSAL OF WASTE (10)

54. (10.1) There should be written procedures for the safe and documented storage and disposal of waste, disposable and rejected items (e.g. contaminated units, units from infected donors, out of date blood, plasma, intermediate or finished products).

## QUALIFICATION AND VALIDATION

### I. PRINCIPLE

1. This Annex describes the principles of qualification and validation which are applicable the manufacture of medicinal products. In order to prove that the parameters of critical processes (equipment) meet the specified requirements, manufacturers need validate the processes and equipment used in the manufacture of medicinal products. Validation is also carried out with significant changes in facilities, equipment and processes that may affect the product quality. A quality risk management approach should be used to determine the composition and scope of the validation activities.

### II. PLANNING FOR VALIDATION

2. All validation activities should be planned. The key elements of validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document.

3. The Validation Master Plan should be a summary document compiled in a concise, transparent and clear form.

4. The VMP includes, in particular, the following information:

- a) (a) validation goal;
- б) (b) organizational structure of validation activity;
- в) (c) summary of the facilities, equipment, systems, processes subject to validation
- г) (d) documentation in the form that should be used for protocols and reports;
- д) (e) activities planning and schedule;
- е) (f) changes control;
- ж) (g) reference to existing documents.

5. For large projects, drawing up of separate validation plans may be necessary.

### III. DOCUMENTATION

6. It is necessary to develop a written protocol with instructions on how qualification and validation will be carried out. Such protocol should be verified and approved. The protocol should include the critical steps and acceptance criteria

7. A report with cross-references to qualification and (or) validation protocol should be prepared where the results obtained, containing comments on any observed deviations, and conclusions, including the recommended changes needed to correct the deviations are summarized. Any changes to the plan given in the protocol, should be formally documented and scientifically justified.

8. A formal release for the next stage in the qualification and validation process should be authorised after successful completion of the qualification programme.

#### IV. QUALIFICATION

##### Design qualification

9. The first element of the validation of new facilities, systems or equipment is the design qualification.
10. The compliance of the design with the [Practice](#) should be demonstrated and documented.

##### Installation Qualification (IQ)

11. The installation qualification should be carried out for new or modified facilities, systems and equipment.
12. The installation qualification should include, but is not limited to the following:

a) (a) verification of the correct installation of components, instrumentation, equipment, pipe work and services for compliance with the approved design, including the production documents, engineering drawings and specifications;

b) (b) completeness evaluation and collation of supplier operating and working instructions and maintenance requirements;

b) (c) evaluation of requirements to calibration of instrumentation;

r) (d) verification of the materials of construction.

##### Operational qualification (OQ)

13. OQ normally follows IQ.

14. OQ should include but is not limited to the following:

a) (a) Tests that have been developed from the knowledge of processes, systems and equipment;

b) (b) Tests to confirm upper and lower operating limits, and /or "worst case" conditions.

15. The completion of a successful OQ should allow the finalisation of standard operating and cleaning procedures, operator training and preventative maintenance requirements. Acceptance of the facilities, systems and equipment can be performed by the customer only after that finalisation.

##### Performance qualification (PQ)

16. PQ should normally follow the successful completion of IQ and OQ.

17. PQ should include, but is not limited to the following:

a) (a) Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions developed on the basis of knowledge of the process and facilities, systems or equipment;

b) (b) Tests under operating parameters equal upper and lower operating limits,

18. While PQ is considered as a separate step of activities, in some cases, it is advisable to perform PQ together with OQ.

##### Qualification of installed (used) facilities, premises and equipment

19. It is necessary to have data that justify and confirm the compliance of critical process parameters with the specified requirements. Instructions for calibration, cleaning, preventive maintenance and operation, as well as operator training and reporting instructions should be documented.

## V. PROCESS VALIDATION

### General

20. Principles and guidelines outlined in this Annex are applicable to the manufacture of all pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes, and re-validation.

21. Usually, the process validation, should be completed before the medicinal product sales start (prospective validation). In exceptional circumstances, where such a validation programme cannot be performed, it may be appropriate to perform process validation during routine production (concurrent validation). Processes that have already been conducted for some time are also subject to validation (retrospective validation).

22. Facilities, systems, and equipment being in use, should be qualified and analytical test methods should be validated. Validation activities should only be performed by suitably trained personnel.

23. Facilities, systems, equipment and processes are subject to routine assessment procedure to confirm their compliance with the specified requirements.

### Prospective validation

24. Prospective validation should include, but are not limited to the following:

- a) (a) summary of the process;
- б) (b) list of critical process stages to be investigated;
- в) (c) list of the equipment/facilities to be used (including measuring/ monitoring/ recording equipment) together with the calibration status;
- г) (d) specifications for finished products when released;
- д) (e) List of analytical methods, as appropriate;
- е) (f) Proposed in-process controls with acceptance criteria;
- ж) (g) additional testing to be carried out with acceptance criteria and analytical methods validation, as appropriate;
- з) (h) sampling plan;
- и) (i) methods for recording and evaluating results;
- к) (j) roles and responsibilities;
- л) (k) estimated schedule of activities.

25. In the traditional approach, a number of batches of the finished product are manufactured under routine conditions (using components that comply with specifications). Theoretically, the number of campaigns performed and the experience gained should be sufficient to allow the normal range of variation and trends to be established and provide sufficient data for evaluation. It is generally considered acceptable that a minimum of three consecutive batches manufactured (campaigns performed) under routine conditions could constitute a validation of the process.

26. Batch size under validation should be the same as batch size at product release to market.

27. If the sale or delivery is planned relating to the batches manufactured under validation, the conditions under which they are produced should fully comply with the marketing authorisation and the requirements of the [Practice](#), including satisfactory outcome of the validation.

#### Concurrent validation

28. In exceptional circumstances, it may be acceptable to start routine production before validation programme is completed.

29. However, the decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.

30. The requirements to concurrent validation documentation are the same as for prospective validation.

#### Retrospective validation

31. Retrospective validation can be performed only for processes shown to be robust. Retrospective validation approach should not be applied when product composition, process or equipment have been recently modified.

32. Retrospective validation of mentioned processes is based on historical data. Additionally, a special protocol and a corresponding report should be prepared as well as the review of previous performance data is prepared with conclusion and recommendations made.

33. Sources from which data supporting such validation were obtained should include, but is not limited to data sources for such validation should include, but are not limited to, batch production and packaging records, production checklists, maintenance logs, personnel changes data, process capability studies, finished product data, including trend maps, as well as the results of studying its storage stability.

34. Batches selected for retrospective validation should be representative sampling for all batches manufactured during the period under review, including all batches that do not meet the specifications. A number of batches should be sufficient in order to prove the process stability. For retrospective validation of the process, additional tests of retained samples may be necessary to obtain the required quantity or necessary type of data.

35. To assess the stability of the manufacturing processes in retrospective validation approach, it is necessary to evaluate data obtained from 10 to 30 consecutively produced batches. However, reducing the number of batches is possible under robust justifications.

### VI. CLEANING VALIDATION

36. Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure. The justification for the selected limits for the carryover of product residues, cleaning agents as well as for microbial contamination should be based on properties of materials used. The limits should be achievable and verifiable.

37. Validated analytical test methods should be applied to detect residues or contaminants. Detection limit for each analytical method should be sufficient in order to detect maximum allowable carryover level of residue or contaminant.

38. As a rule, cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment surfaces. However, some consideration should be also given to the equipment components not being in direct contact with products. Validation exercise needs to be performed for length of time between the end of manufacturing process and cleaning, and the time between cleaning and the beginning of the next process. Cleaning methods should be defined as well as intervals between cleaning exercises.

39. For cleaning procedures related to very similar products and processes, it is acceptable to select a representative range of similar products and processes. In such cases, one validation study can be conducted using the "worst case" approach, which takes into consideration all the critical parameters.

40. For cleaning validation exercise, it is quite enough to carry out three successful consecutive cleaning cycles.

41. Repeated cleaning and retesting "until it is clean" cannot replace cleaning validation exercise.

42. If the substances to be removed are toxic or hazardous, then, as an exception, they can be replaced by medicines that simulate the physicochemical properties of such substances.

## VII. CHANGE CONTROL

43. Written procedures should be in place to describe the actions to be taken if a planned change is proposed to a starting material, product component, equipment, process environment (site) parameters, method of production or testing, or any other change during the life cycle that may affect product quality or reproducibility. Change control procedures should ensure that sufficient data is obtained to confirm that the changes to process ensure the desired product quality, corresponding to the approved specifications.

44. Applications must be submitted within the framework of the pharmaceutical quality system for all planned changes which may affect the quality of the product or reproducibility. Such changes should be formally documented and approved. Any planned changes to the facilities, systems and equipment, which may affect the quality of the product should be assessed including the risk assessment. Need and scope of re-qualification and re-validation should be determined.

## VIII. RE-VALIDATION

45. Regular verification of facilities, systems, equipment and processes including cleaning procedures should be performed against pre-defined criteria. In the absence of significant changes, re-validation can be replaced by drawing a report being a written evidence that facilities, systems, equipment and processes comply with pre-defined criteria.

## IX. TERMS AND DEFINITIONS

The following basic concepts are also used in the context of this Annex except for the terms and definitions defined in [Chapter II](#) of the Practice:

risk assessment - a method of assessment and description of critical operating parameters for equipment, system or process in connection with the determined hazard;

cleaning validation - formally documented evidence that approved cleaning procedure is able to ensure such cleanliness of equipment which is appropriate for manufacture of medicinal products;

process validation is a documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes;

Installation Qualification (IQ) - the documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Design qualification (DQ) - The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

Operational qualification (OQ) - the documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges;

Performance Qualification (PQ) The documented verification that facilities, systems and equipment can perform effectively and reproducibly based on the approved process method and parameters.

Change Control. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes.

The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.

Simulated agents. A material that closely approximates the physical and, where practical, the chemical characteristics, e.g. viscosity, particle size, pH etc., of the product under validation. In many cases, a batch of placebo (product without active substance) may have such properties;

Worst Case A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

Prospective Validation. Validation carried out before routine production of products intended for sale;

Re-validation. Repeated process validation to ensure that changes in process and (or) equipment made in accordance with changes control do not have adverse effect on process characteristics and product quality;

Retrospective validation. Validation of routine production of the marketable product based on data gathered concerning batches manufacture and control;

Concurrent Validation. Validation performed during routine production of products intended for sale

Annex No. 16  
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## CERTIFICATION BY A QUALIFIED PERSON AND BATCH RELEASE

### I. SCOPE (1)

1. (1.1) This Annex provides guidance on the certification by a Qualified Person (QP) and on batch release related to medicinal products intended to be placed on the national market holding a marketing authorisation (MA) or made for export.

2. (1.2) This Annex also covers the cases when batch production or testing is divided into several stages conducted in different sites or by different manufacturers as well as the cases when intermediate or bulk batch is divided into two or more batches of finished products. This Annex can apply to medicinal products intended for clinical trials.

3. (1.3) If the regulatory legal acts of the Russian Federation establish special requirements for putting of some blood and immunobiological medicinal products on market, such requirements must be observed.

4. (1.4) The basic arrangements for batch release for a product are defined by its marketing authorisation, Manufacturing Formulae and specification. Nothing in this Annex should be taken as overriding those arrangements.

### II. PRINCIPLE

5. (2.1) the QP is responsible for ensuring that each individual batch of finished products has been checked and received confirmation of compliance with the established requirements before being released for sale or for export.

6. (2.2) The purpose of controlling batch release is to ensure that:



The batch has been manufactured and checked before its release, in accordance with the license for the production of medicinal products, the requirements of its MA, guidelines of this [Practice](#), and any other relevant legal requirements of the Russian Federation;

In the event that a quality defect needs to be investigated or a batch recalled, to ensure that any QPs involved in the certification, and any relevant records are readily identifiable.

### III. INTRODUCTION (3)

7. (3.1) Batch manufacture including, quality control is divided into several stages which may be at several sites and by different manufacturers. Each step should be carried out in accordance with the requirements of Manufacturing Formulae, guidelines of this [Practice](#) and other regulatory legal acts of the Russian Federation. The QP, who confirms compliance for finished product batch with the established requirements before its release, must be guided by the mentioned requirements.

8. (3.2) In practice, one QP may not have detailed knowledge of the manufacturing process steps. The QP, confirming compliance for the finished product batch, is entitled to rely on conclusions of other QPs concerning specified steps. In such cases, the QP should be sure in advance that such conclusions are reliable, based on her/his personal experience or confirmation obtained from other QPs within the established quality system.

9. (3.3) When individual steps are carried out in a third country, a production participant in the third country should comply with similar requirements to the manufacture and control of a batch. In this situation, medicinal products should be produced in accordance with the requirements of MA. The manufacturer should have an authorization (licence) to perform its activities in accordance with laws of his country and comply with the requirements of this [Practice](#), or Good Manufacturing Practice (GMP) for medicinal products, at least equivalent to that referred in this [Practice](#).

### IV. GENERAL (4)

10. (4.1) There may be several sites involved in the various stages of manufacture, importation, testing and storage of a batch before its release. All these sites should undergo certification and be controlled by at least, one QP, confirming compliance of the batch with the established requirements, before its release. Regardless of how many sites are involved, the QP must keep production of an individual batch under her/his general supervision and confirm the compliance of this finished product batch with the established requirements before release.

11. (4.2) Different batches may be manufactured, imported or released in other countries that concluded Mutual Recognition Agreements with the Russian Federation. In this case, the MA holder as well as each site entitled to release product batch, should have exact address of the site where a specified batch was released, and details of QP who is responsible for confirmation of compliance of the batch quality with established requirements.

12. (4.3) QP confirming the compliance of a finished product batch with the established requirements before its release, can make their decision based on her/his personal knowledge of all facilities and processes used in production, the experience of personnel involved in the manufacture and the applicable quality system within which production is carried out. The specified QP may also rely on the conclusion of one or more QPs concerning the compliance of the intermediate production stages with the established requirements.

13. Such a conclusion issued by other qualified persons must be documented and must clearly define the subject of confirmation of compliance. The confirmation procedure should be formally documented.

14. (4.4) The confirmation procedure, mentioned in [item 13](#) of this Annex, shall be observed in all cases when QP relies on the conclusion of another QP. Such a document must comply with the provisions of [items 237 - 255](#) of this Practice. QP certifying a finished product batch being in accordance with the established requirements, must guarantee the conducting of the activities specified in this document. The form of the document, in relation to compliance of a batch must correspond to the mutual relations of the parties. For example, such a document could be a standard operating procedure for a manufacturer or an agreement between different manufacturers, even if they are part of the same group of companies.

15. (4.5) The said contract between manufacturers includes the obligation on the part of the bulk or

intermediate product supplier to notify the recipient (s) of the product of any deviations, confirmed out of specification results, noncompliance with the requirements of this [Practice](#), investigations, complaints or other events, which must be taken into account by QP responsible for confirmation of compliance of a finished product batch with all established requirements.

16. (4.6) If a computerised system is used to formalise the confirmation of compliance and batch release, a particular attention should be paid to observance of the requirements given in [Annex No. 11](#) to the Practice.

17. (4.7) If there is evidence of confirmation of compliance of a finished product batch issued by QP, this procedure does not need to be repeated in countries that have with the Russian Federation an Mutual Recognition Agreement in relation to results of such procedure.

18. (4.8) Regardless of the specific activities for confirmation and batch release, there should be a procedure for a rapid identification and recall of all products that may pose a hazard to consumers.

#### V. TESTING AND RELEASE OF BATCH OF PRODUCTS MANUFACTURED IN THE RUSSIAN FEDERATION (5)

19. (5.1) If the production is located on one certified site of manufacture:

If all stages of manufacture and control are carried out on the same site, the performance of individual audits and control operations can be outsourced to third persons. QP of this site of manufacture, confirming the conformity of a batch of finished products, usually bears personal responsibility for the reliability of the audit results within the established quality system. However, QP may also take into account the conclusions on the compliance with the established requirements of intermediate stages issued by other QPs on this site who are responsible for these stages.

20. (5.2) If several sites involved in the various stages of manufacture:

If the various stages of manufacture of a batch are carried out on different sites within a single establishment, regardless of the fact whether the same licence (manufacturer's authorisation) covers all of batches or not, QP must assume responsibility for every stage of manufacture. Confirmation of conformity of a finished product batch to the established requirements should be carried out by QP of the manufacturer who either bears personal responsibility for all stages of manufacture, or takes into account the conclusions about the previous stages made by the QPs responsible for these stages.

21. (5.3) If specified intermediate stages of manufacture are carried out under a contract by another establishment:

One intermediate stage or more of manufacturing process and quality control may be performed by other contractor in accordance with the provisions set out in [paragraphs 237 - 255](#) of this Practice. QP of the customer may take into consideration a conclusion of the contractor's QP about the relevant stage, but QP is responsible for ensuring compliance for those operations with the terms of the contract. The manufacturer's QP, responsible for batch release, should provide confirmation of compliance of the finished product batch with the relevant requirements.

22. (5.4) If several batches of finished products, released on the market on the basis of one marketing authorisation (MA) are manufactured from a bulk batch on different sites:

a) (5.4.1) QP of the Manufacturer having a licence (manufacturer's authorisation) for the manufacture of medicinal products and producing a bulk batch may confirm the conformity of all finished product batches before their release. In this case, QP either bears personal responsibility for all stages of manufacture, or takes into account the conclusions in relation to filling and (or) packaging stages made by the QPs of the sites where for these stages have been carried out;

b) (5.4.2) It is also possible to provide confirmation of compliance of each finished product batch before its release by QP of the manufacturer who performed the final filling and (or) packaging operation. In this case, QP either bears personal responsibility for all stages of manufacture, or takes into account the conclusion in relation to

batch quality made by the QP of the site where bulk batch is released;

b) (5.4.3) In all cases where finished products are manufactured in different places at different production sites under the same registration marketing authorisation, one person (usually QP of the manufacturer of a bulk batch) who is solely responsible for release of all finished product batches obtained from the same bulk batch. This person should be aware of any challenges related to the quality of any finished product batch and coordinate all necessary activities performed to solve challenge in connection with bulk batch.

In spite of the fact that the numbers of bulk and finished batches do not necessarily have to match, it is necessary to document the connection between numbers of these batches so that you can provide follow-up during the audit.

23. (5.5) In case where several batches of finished products are filled and (or) packaged from the same bulk batch in different places at different production sites and released under the different marketing authorisations, (as is the case, for example, when a transnational company owns national marketing authorisations for a medicinal product in several states, or the manufacturer of reproduced medicines acquires a bulk drug, fills and (or) packs it, and then, releases a finished product under its own MA):

a) (5.5.1) QP of the finished product manufacturer who confirms the compliance of finished product batch with established requirements, either takes sole responsibility for all stages of manufacture, or takes into consideration the conclusion made by QP of bulk product manufacturer;

b) (5.5.2) Any problem related to the quality of any batch of finished products, the source of which could be the initial bulk batch, shall be notified to QP responsible for confirming the quality of this bulk batch. After this, the specified QP must take all necessary measures with respect to all batches of finished products made from this bulk batch. The procedure in this case should be set in the agreement.

24. (5.6) If a finished product batch is purchased and sold by a manufacturer having a licence to manufacture medicinal products in accordance with its own marketing authorisation (as is the case, for example, when the manufacturer supplying the reproduced medicinal product is the holder of MA for a medicine manufactured by another manufacturer), and the first manufacturer purchases finished products, the conformity of which has not yet been confirmed by its manufacturer, and releases it on the basis of his own licence (manufacturer's authorisation) to manufacture medicines and his own MA:

The manufacturer's QP who buys the product and does not have documentary results of confirmation of its compliance must itself confirm compliance with the established requirements for this finished product batch before it is released. In this case, QP of the procuring manufacturer assumes responsibility for all stages or relies on the conclusion on the batch quality made by QP of the manufacturer-supplier.

25. (5.7) If the laboratory of quality control for medicinal products and the manufacturer are different establishments:

QP confirming the conformity of a finished product batch with the established requirements may take responsibility for laboratory tests conducted by such a laboratory, or rely on the test confirmation issued by another qualified person. In the absence of such confirmation, QP must have the detailed knowledge of the activities in this laboratory and the methods used to confirm the conformity of the quality of this finished product.

## VI. QP RESPONSIBILITIES (6)

26. (6.1) Before carrying out the confirmation of conformity for a finished product batch until its release, QP should ensure, in particular, of meeting the following requirements:

a) (a) The finished product batch itself and its manufacturing process in compliance with the provisions of regulatory documents;

b) (b) finished product batch is manufactured in accordance with the requirements of this [Practice](#), and for a batch imported from other countries - in accordance with the guidelines of Good Manufacturing Practice (GMP) for medicinal products, at least equivalent to that referred in this [Practice](#);

в) (c) key manufacturing processes and control methods are validated, actual production conditions and batch records are taken into consideration;

г) (d) any deviations or planned changes in manufacturing process or quality control have been approved by authorised persons, appropriate competent federal executive body is aware of any changes which need to be introduced in the MA or license for the manufacture of medicines; permission of the competent federal executive body to make such changes is obtained;

д) (e) all necessary tests or checks (including additional sampling, audit, checks and tests, caused by deviation in manufacturing process or due to planned changes) are made;

е) (f) the documentation in relation to manufacturing process and quality control is drawn up and approved by authorised personnel;

ж) (g) All audits have been carried out in accordance with the quality assurance system;

з) (h) all the factors that, in the opinion of QP, are essential for the quality of this batch, are taken into consideration.

27. QP may have additional duties in accordance with the legislation of the Russian Federation or job descriptions approved by the manufacturer.

28. (6.2) QP, confirming the conformity of the intermediate stage of manufacturing in accordance with [items 12 - 13](#) of the Annex, shall perform duties similar to those specified above with respect to this stage.

29. (6.3) QP shall maintain his / her qualification at the present level in the light of scientific and technical progress achievements and take into account changes in the quality management system relevant to products whose conformity to the established requirements is confirmed by QP.

30. (6.4) When a QP is involved in confirming the compliance of a batch of products that he does not know enough (for example, when developing a new type of product or moving to another enterprise), QP must obtain the relevant knowledge and experience necessary to fulfill these duties.

31. In accordance with the regulatory legal acts of the Russian Federation, QP may be assigned to notify the authorized federal executive body of such a change that it may require re-certification.

## VII. TERMS AND DEFINITIONS (7)

32. For the purposes of this Annex, in addition to the terms and definitions provided for in [Chapter II](#) of this Practice, the following basic concepts are also used:

Certification of the finished product batch - represents the quality release of the batch before the batch is released for sale or distribution that is formally documented.

Confirmation - a signed statement by a QP that a process or test has been conducted in accordance with the requirements of [the GMP](#) and Quality Control and the relevant marketing authorisation, as agreed in writing with the QP responsible for certifying the finished product batch before release.

Finished product batch - the batch of product in its final pack for release to the market;

Bulk product batch (bulk batch) - a batch of products of size defined at certification (registration) of a medicinal product, ready for filling, final packaging, or being in individual packs and ready for completion of final packs. A bulk batch may contain, for example, a liquid bulk product, solid dosage forms (tablets or capsules), or filled ampoules;

Mutual Recognition Agreement - an agreement on mutual recognition of audits with a country in which imported medicines are produced (from which they are supplied).

## PARAMETRIC RELEASE

### I. PRINCIPLE (1)

1. (1.1) Parametric release is a product release system that ensures that the products are of the required quality, based on information obtained during the manufacturing process, and also on the basis of compliance with certain requirements of this [Practice](#), relating to parametric release.

2. (1.2) Parametric release should meet the basic requirements of this [Practice](#), including the relevant Annexes thereto and the requirements set out below.

### II. PARAMETRIC RELEASE (2)

3. (2.1) Carrying out a comprehensive set of checks and monitoring parameters in the manufacturing process can provide a higher guarantee of compliance for the finished product with specification compared to the testing of the finished product.

4. (2.2) Parametric release may be authorised with respect to certain special parameters as an alternative to the traditional finished product test. There are officials of authorised federal executive bodies who are entitled to jointly approve parametric release, deny or revoke their permit for parametric release. Such officers are responsible for assessing products during marketing authorisation registration and conducting audits to comply with this [Practice](#).

### III. PARAMETRIC RELEASE FOR STERILE PRODUCTS (3)

5. (3.1) In [paragraphs 5 - 21](#) of this Annex, there are set out the requirements for parametric release for the finished product without passing the test for sterility. Waiving the performance of a test for sterility is valid only on the basis of successful demonstration that predetermined and validated sterilising conditions have been achieved.

6. (3.2) Testing for sterility only provides an opportunity to detect major failures in the sterility assurance system.

7. (3.3) Parametric release is allowed only if the parameters of the sterilisation process for a product batch guarantee that the validated sterilisation process ensures the product sterility.

8. (3.4) Parametric release is permitted only for medicinal products subject to final sterilisation in the primary packaging.

9. (3.5) For parametric release, sterilisation methods may be considered that provide for use of steam, dry heat and ionizing radiation in accordance with the monographs of the State Pharmacopoeia of the Russian Federation.

10. (3.6) Parametric release does not apply to the manufacture of entirely new medicinal products, since satisfactory results of tests for sterility over a period of time are part of the acceptance criteria. In some cases, these tests for sterility, already available for other drugs, can be considered sufficient for a new medicinal product, in which only a slight change has been made in terms of ensuring sterility.

11. (3.7) The assessment of risks in the sterility management system need to be performed in order to evaluate the risk of the release of non-sterile products.

12. (3.8) Previous experience of the manufacturer of medicinal products should indicate the compliance of its

production with the requirements of this [Practice](#).

13. (3.9) When assessing the conformity of manufacturing with the requirements of this [Practice](#), the detected cases of violation of sterility shall be taken into account, as well as the results of tests for sterility of the medicinal product in question in terms of drugs sterilised in the same or a similar way.

14. (3.10) The production and sterilisation site must be provided by a qualified engineer with experience in sterility management and a qualified microbiologist.

15. (3.11) The development and initial validation of the product shall ensure that, subject to all appropriate conditions, products of the same quality will be released.

16. (3.12) The change control system should provide for their analysis by the personnel providing sterility.

17. (3.13) It is necessary to organize a control system for microbial contamination of a medicinal product before sterilisation.

18. (3.14) The potential mix up of products that have passed and not passed sterilisation should be avoided, which is ensured by physical separation of products or use of validated electronic systems.

19. (3.15) Sterilisation records shall be verified for compliance with the specifications, involving at least two independent monitoring systems. Such control can be carried out by two employees or an employee and a validated computer system.

20. (3.16) Before the release of each batch of products, it is necessary to further confirm the following:

all scheduled maintenance and routine checks of the steriliser used are performed;

all repair work and changes are coordinated with engineer and microbiologist who are responsible for the sterilisation process;

the devices used were calibrated (verified);

the validity period of the steriliser for this load has not expired.

21. (3.17) If a permit is issued for the parametric release of a product batch, then decisions on the release or rejection of the batch should be based on the requirements of the approved instructions in the part of the parametric release. If these requirements are not met, the parametric release is not allowed, even if the test for sterility is successfully carried out.

#### IV. TERMS AND DEFINITIONS

22. For the purposes of this Annex, the following basic concepts are used:

parametric release - a system of product release that ensures that the product is of the required quality, on the basis of information obtained during the manufacturing process and in accordance with specific rules for the organization of production and quality control of medicinal products associated with parametric release;

Sterility system - a set of measures to ensure the sterility of products. For medicinal products subject to final sterilisation, this set of measures includes the following:

a) (a) development of a medicinal product;

b) (b) knowledge and, where possible, control of the microbiological characteristics of the starting material and process aids (eg, gases and lubricants);

b) (c) contamination control measures taken during the process to prevent microbes from entering in products and their multiplication, which is usually achieved by cleaning and sanitisation of surfaces in contact with products, preventing contamination from air by conducting process operations in clean premises, with time

limitations and, where appropriate, the use of filtration steps;

г) (d) prevention of mix up between flows of sterilised and unsterilised products;

д) (e) constant achievement of product quality;

е) (f) sterilisation;

ж) (g) quality system as a whole, including the sterility management system, namely: changes control, staff training, availability of manufacturer-approved instructions, release control, scheduled maintenance, fault analysis, prevention of human errors, validation, calibration (verification).

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## REFERENCE AND RETAINED SAMPLES

### I. SCOPE (1)

1. (1.1) This Annex gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.

2. (1.2) Specific requirements for investigational medicinal products are given in [Annex 13](#) to this Practice.

3. (1.3) This Annex also includes guidance on the taking of retention samples for parallel imported/distributed medicinal products.

### II. PRINCIPLE

4. (2.1) Samples are retained to fulfil two purposes: firstly to provide a sample for analytical testing and secondly to provide a specimen of the fully finished product. Samples may therefore fall into two categories:

Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned. Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates, that are transported outside of the manufacturer's control, should be kept.

Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned. There may be exceptional circumstances where this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.

5. For finished products, in many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

6. (2.2) It is necessary for the manufacturer, importer or site of batch release, as specified under [items 20 - 25](#) of this Annex), to keep reference and/or retention samples from each batch of finished product and, for the manufacturer to keep a reference sample from a batch of starting material (subject to certain exceptions in [item 10](#) of the Annex) and (or) intermediate product. Each packaging site should keep reference samples of each batch of primary and printed packaging materials. Availability of printed materials as part of the reference and/or retention sample of the finished product can be accepted.

7. (2.3) The reference and/or retention samples serve as a record of the batch of finished product or starting material, an Appendix to the batch record, and can be assessed in the event of, for example, a dosage form quality complaint, a query relating to compliance with the marketing authorisation, a labelling/packaging query or a pharmacovigilance report (a query of the authorised federal executive body).

8. (2.4) Records of traceability of samples should be maintained. They should be available for review by competent authorities.

### III. STORAGE DURATION (3)

9. (3.1) Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference sample should be contained in its finished primary packaging. In case the primary packaging is very large, the reference sample can be packaged in packaging composed of the same material as the primary container in which the product is marketed. The relevant guidance for veterinary medicinal products other than immunologicals prepared to be imported see in [items 5 - 6](#) of Annex No. 4 to this Practice.

10. (3.2) Unless a longer period is required under the appropriate regulatory legal acts of the Russian Federation, samples of starting materials (other than solvents, gases or water used in the manufacturing process) shall be retained for at least two years after the release of product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. Packaging materials should be retained for the duration of the shelf life of the finished product concerned.

### IV. SIZE OF REFERENCE AND RETENTION SAMPLES (4)

11. (4.1) The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the Marketing Authorisation File which has been assessed and approved by the relevant Competent Authority / Authorities. Where it is necessary to do so, unopened packs should be used when carrying out each set of analytical controls. Any proposed exception to this should be justified to, and agreed with, the relevant federal executive authority.

12. (4.2) Where applicable, the requirements of the regulatory legal acts of the Russian Federation relating to the size of reference samples and, if necessary, retention samples, should be followed.

13. (4.3) Reference samples should be representative of the batch of starting material, intermediate product or finished product from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). Where a batch is packaged in two, or more, distinct packaging operations, at least one retention sample should be taken from each individual packaging operation. Any proposed exception to this should be justified to, and agreed with, the relevant federal executive authority.

14. (4.4) It should be ensured that all necessary analytical materials and equipment are still available, or are readily obtainable, in order to carry out all tests given in the specification until one year after expiry of the last batch manufactured.

### V. STORAGE CONDITIONS (5)

15. (5.1) Storage of reference samples of finished products and active substances should be in accordance with the requirements of regulatory legal acts of the Russian Federation.

16. (5.2) Storage conditions should be in accordance with the marketing authorisation (e.g. refrigerated storage where relevant).

### VI. WRITTEN AGREEMENTS (6)

17. (6.1) Where the marketing authorisation holder is not the same legal entity as the site(s) responsible for batch release within the Russian Federation, the responsibility for taking and storage of reference/retention samples should be defined in a written agreement between the two parties in accordance with [paragraphs 237 - 255](#) of this Practice. This applies also where any manufacturing or batch release activity is carried out at a site



other than that with overall responsibility for the batch on the Russian market. The arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement between the manufacturers-owners of these sites.

18. (6.2) The Qualified Person who certifies a batch for sale should ensure that all relevant reference and retention samples are accessible at all reasonable times. Where necessary, the arrangements for such access should be defined in a written agreement.

19. (6.3) Where more than one site is involved in the manufacture of a finished product, the availability of written agreements is key to taking and location of reference and retention samples.

#### VII. REFERENCE SAMPLES GENERAL POINTS (7)

20. (7.1) Reference samples are for the purpose of analysis and, therefore, should be conveniently available to a laboratory with validated methodology. For starting materials used for medicinal products manufactured within the RF, this is the original site of manufacture of the finished product. For finished products manufactured within the RF, this is the original site of manufacture.

21. (7.2) For finished products manufactured by a manufacturer in a country outside the Russian Federation:

a) (7.2.1) where an operational Mutual Recognition Agreement (MRA) between the Russian Federation and that state is in place, the reference samples may be taken and stored at the site of manufacture. This should be covered in a written agreement (as referred to in [items 17 - 19](#) of this Annex) between the importer/site of batch release within the Russian Federation and the manufacturer located outside the RF;

b) (7.2.2) where an operational MRA is not in place, reference samples of the finished medicinal product should be taken and stored at an authorised manufacturer located within the Russian Federation. These samples should be taken in accordance with written agreement(s) between all of the parties concerned. The samples should, preferably, be stored at the location where testing on importation has been performed.

b) (7.2.3) reference samples of starting materials and packaging materials should be kept at the original site at which they were used in the manufacture of the finished medicinal product.

#### VIII. RETENTION SAMPLES. GENERAL POINTS (8)

22. (8.1) A retention sample should represent a batch of finished products as distributed in the Russian Federation and may need to be examined in order to confirm non-technical attributes for compliance with the marketing authorisation or other requirements of the regulatory legal acts of the Russian Federation. Therefore, retention samples should preferably be stored at the site where the Qualified Person (QP) certifying the finished product batch is located.

23. (8.2) In accordance with [item 22](#) above, where an operational MRA is in place and reference samples are retained at a manufacturer located in a country outside the Russian Federation ([see subitem "a" of item 21](#) above), separate retention samples should be kept within the Russian Federation.

24. (8.3) Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the authorised federal executive body.

25. (8.4) Where more than one manufacturing site within the Russian Federation is involved in the manufacture importation/ packaging/ testing/ batch release, as appropriate of a product, the responsibility for taking and storage of retention samples should be defined in a written agreement(s) between the parties concerned.

#### IX. REFERENCE AND RETENTION SAMPLES FOR PARALLEL IMPORTED/ PARALLEL DISTRIBUTED PRODUCTS (9)

26. (9.1) Where the secondary packaging is not opened, only the packaging material used needs to be retained, as there is no, or little, risk of product mix up.

27. (9.2) Where the secondary packaging is opened, for example, to replace the carton or patient information leaflet, then one retention sample, per packaging operation, containing the product should be taken, as there is a risk of product mix-up during the assembly process. It is important to be able to identify quickly who is responsible in the event of a mix-up (original manufacturer or parallel distribution assembler), as it would affect the extent of any resulting recall.

#### X. REFERENCE AND RETENTION SAMPLES IN THE CASE OF CLOSEDOWN OF A MANUFACTURER (10)

28. (10.1) Where a manufacturer closes down and the manufacturing licence (authorisation) is surrendered, revoked, or ceases to exist, it is probable that many unexpired batches of medicinal products manufactured by that manufacturer remain on the market. In order for those batches to remain on the market, the manufacturer should make detailed arrangements for transfer of reference and retention samples (and relevant [GMP](#) documentation) to an authorised storage site. The manufacturer should satisfy the Competent Federal Authority that the arrangements for storage are satisfactory and that the samples can, if necessary, be readily accessed and analysed.

29. (10.2) If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The Marketing Authorisation holder (MAH) is responsible for such delegation and for the provision of all necessary information to the Competent Federal Executive Authority. In addition, the MAH should, in relation to the suitability of the proposed arrangements for storage of reference and retention samples, consult with the competent federal executive authority.

30. (10.3) These requirements apply also in the event of the closedown of a manufacture located outside the Russian Federation. In such instances, the importer has a particular responsibility to ensure that satisfactory arrangements are put in place and that the competent federal executive authority is consulted.