COLLEGIATE BOARD RESOLUTION – RDC NO. 658 OF 30 MARCH 2022

Provides for the General Guidelines on the Good Manufacturing Practices for Medicinal Products

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, item III of Law no. 9,782 of 26 January 1999, and item VI, paragraphs 1 and 3 of Article 187 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Collegiate Board Resolution, as decided upon in the Extraordinary Meeting – RExtra 6, held on 30 March 2022, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 1. This Resolution has the objective of adopting the general guidelines on Good Manufacturing Practices for Medicinal Products of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), as minimum requirements to be followed in the manufacture of medicinal products.

Section II

Scope

Article 2. This Resolution applies to companies that carry out the operations involved in the manufacture of medicinal products, including experimental medicines.

Section III

Definitions

Article 3. For the purposes of this Resolution and the normative instructions linked to it, the following definitions are applied:

I – technical agreement: document that defines responsibilities, attributions, rights, and duties of/ between contractor and contracted party in relation to outsourced activities;

II – corrective action: measures adopted that refer to a reactive containment, to treat and eliminate the root cause of deviation or non-compliance that has already occurred;

III – preventive action: measures adopted, which refer to the proactive mitigation of risks, to avoid the occurrence of a deviation or non-compliance, ultimately seeking to eliminate its causes;

IV – antechamber: closed space with two or more doors, interposed between two or more rooms, for the purpose of controlling the air flow between these rooms when they need to be entered, designed to be used for people, materials, or equipment;

V – clean area: area with defined environmental control of particulate and microbial contamination, constructed and used to reduce the introduction, generation, and retention of contaminants within the area;

VI – plant master file: document that describes the activities related to the manufacturer's good manufacturing practices;

VII – calibration: set of operations that establishes, under specified conditions, the relationship between values indicated by a measuring instrument or system, or values represented by a materialized measurement, and the corresponding known values of a reference standard;

VIII – certificate of analysis: document that provides a summary of the results of tests on samples of products or materials together with the assessment of their compliance with the declared specification, which may, alternatively, be based, in whole or in part, on real-time data evaluation (summaries and exception reports) of batch-related analytical process technology, parameters or metrics, in accordance with the product marketing authorization;

IX – contamination: unwanted introduction of impurities of a chemical or microbiological nature, or foreign matter, into raw material, intermediate product and/ or finished product during sampling, weighing, formulation, production, (re)packing, storage, or transportation stages;

X – cross-contamination: contamination of a certain raw material, intermediate product, bulk product, or finished product by another raw material, intermediate product, bulk product, or finished product during sampling, weighing, formulation, production, (re)packing, and storage stages;

XI – containment: action of confining a biological agent or other substance within a defined space;

XII – in-process control: verifications carried out during production to monitor and adjust the process, environment, and equipment to ensure that the product is in conformity with its specification;

XIII – raw material/ input expiration date: date defined by the manufacturer of such materials, which establishes the time (based on specific stability studies) during which the materials in question remain within the established shelf-life specifications (characterized as the shelf life period), if stored under defined conditions and after which they must not be used;

XIV – product expiration date: date established on the packaging of medicinal products, usually on labels, until which the product is expected to remain within its specifications, provided they are stored correctly, established by batch, adding the expiration date to the manufacturing date;

XV – retest date: date established by the manufacturer of the raw material/ input, based on stability studies, after which the material must be reanalyzed to ensure it is still suitable for use, according to tests indicating the stability defined by the manufacturer of the raw material/ input,

maintaining the pre-established storage conditions, and being only applicable when the expiration date is not established by the manufacturer of the raw material/ input;

XVI – deviation: non-compliance with the requirements determined by the Pharmaceutical Quality Management System or necessary for the maintenance of quality, safety, and efficacy of the products;

XVII – return: shipment of medicinal products back to the manufacturer, which may or may not present a quality defect, after they have been shipped by that manufacturer;

XVIII – packaging: all operations, including filling and labeling, to which the bulk product must be submitted in order to become a finished product;

XIX – specification: document that describes in detail the requirements which products or materials used or obtained during manufacturing must comply with, serving as a basis for quality assessment;

XX – sterility: it is the absence of living organisms, and the conditions of sterility tests are established by the Brazilian Pharmacopoeia, or another pharmacopoeia officially recognized by Anvisa;

XXI – manufacture: all operations involved in the preparation of a particular medicinal product, including procurement of materials, production, quality control, release, storage, shipment of finished products, and the related controls;

XXII – manufacturer: holder of authorization to manufacture medicinal products, in accordance with the health regulations of the country where it is located;

XXIII – (manufacturing, processing, packaging) formulas and (testing) instructions: documents that provide details of all raw materials, equipment, and computerized systems to be used and specify all (packaging, sampling) process and testing instructions;

XXIV – process instructions: documents that specify, in detail, even if in a simple language, how to carry out one of the stages of the processes, aiming at facilitating the execution of routine tasks (from a technical-operational point of view) by operators and analysts, unlike procedures, which generally contain more detailed information and guidelines about the Pharmaceutical Quality System management;

XXV – atypical active pharmaceutical ingredient: excipient, food or cosmetics industry input used in the pharmaceutical industry as an active pharmaceutical ingredient;

XXVI – action limit: established criterion, requiring immediate monitoring and corrective action if exceeded;

XXVII – alert threshold: established criteria that give early warning of potential deviation from normal conditions that are not necessarily grounds for definitive corrective action, but which require follow-up actions;

XXVIII – batch: defined amount of raw material, packaging material, or product processed in one or more processes, the essential characteristic of which is homogeneity, and it may be necessary, in order to complete certain stages of manufacture, to divide a batch into several sub-batches, which are then reunited to form a final homogeneous batch, and, in the case of continuous manufacturing, corresponding to a defined fraction of production, characterized by the intended homogeneity;

XXIX – packaging material: any material used in the packaging of medicinal products, excluding any external packaging used for transportation or shipment, being classified as primary or secondary, according to the degree of contact with the product;

XXX – raw material: any substance used in the production of medicinal products, excluding packaging materials;

XXXI – medicinal product: pharmaceutical product, technically obtained or elaborated, for prophylactic, curative, palliative, or diagnostic purposes;

XXXII – non-compliance: failure to meet a pre-established requirement, which may vary between external and internal factors, and relate, for example, with procedures, standards, legislation, facilities, equipment, systems, processes, products, suppliers, materials, services, method, among others;

XXXIII – batch number: distinctive combination of numbers and/ or letters that specifically identifies a batch;

XXXIV – sponsor: person, company, institution, or organization responsible for the initiation, management, control, or funding of a clinical trial;

XXXV – 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 a medicinal product;

XXXVI – production: all operations involved in the preparation of a medicinal product, from the receipt of materials, through processing and packaging, to completion as a finished product;

XXXVII – finished product: product that has gone through all stages of production, including labeling and final packaging;

XXXVIII – bulk product: any product that has completed all stages of processing up to, but not including, the primary packaging, with sterile products in their primary packaging being considered a bulk product;

XXXIX – intermediate product: partially processed product that must be submitted to subsequent manufacturing stages before becoming a bulk product;

XL – protocol: document that provides instructions on how to execute and record certain discrete operations;

XLI – qualification: action of proving that any facilities, equipment, utilities, and systems work correctly and actually lead to the expected results;

XLII – quarantine: status of raw materials or packaging materials, intermediate products, bulk or finished products, physically separated, not necessarily in separate environments, or through other effective means, pending a decision on their release or refusal;

XLIII – reanalysis: analysis performed on raw material/ input, previously analyzed and approved, to confirm the maintenance of the specifications established by the manufacturer, within the validity period;

XLIV – reconciliation: comparison, considering the normal variation, between the theoretical and actual quantity of products or materials produced or used;

XLV – recovery: introduction of all or part of previous batches of required quality into another batch at a defined stage of manufacture;

XLVI – record: document that provides evidence of the actions taken to demonstrate the compliance with instructions – e.g., activities, events, investigations and, in the case of manufactured batches, a history of each batch of the product, including its distribution – including the raw data used to generate other records, and all data on which quality decisions are based are considered as raw data;

XLVII – report: documentation that records the conduct of exercises, projects, and specific investigations, together with the results, conclusions, and recommendations;

XLVIII – reprocess: operation of all or part of a product batch, of unacceptable quality, from a defined production stage, so that its quality can be accepted after carrying out one or more additional operations;

XLIX – Technical Responsible Officer: professional recognized by the national regulatory authority who is responsible for ensuring that each batch of finished product has been manufactured, tested, and approved for release in accordance with the laws and regulations in force in the country;

L – label: printed or lithographed identification, as well as painted or fire engraved words, or engraved through pressure or decal, applied directly on containers, wrappers, wraps, or any other packaging protector;

LI – simulation of the aseptic process: method of evaluation of an aseptic process through a microbial growth medium, considering media filling as synonyms, for example, simulated product fillings, medium tests, filling tests, among others;

LII – Corrective Action and Preventive Action (CAPA) system: work process, in which different tools can be used, both for quality management and risk management, which apply to identification, the evaluation and investigation of past events (deviations, non-conformities, etc.), the definition of the action plan, the implementation of the actions defined in the action plan and, finally, the verification of the effectiveness of the actions (both corrective and preventive) implemented, or to stop the root cause of past events (deviations, nonconformities, etc.), avoiding recurrences, or to prevent the occurrence of future events (deviations, nonconformities, etc.), and referring to a quality system component that, being conducted consistently and effectively by the company, has the power to assist in the promotion of continuous improvement of the Pharmaceutical Quality System;

LIII – computerized system: system that includes data entry, electronic processing, and the output of information to be used for reporting or automatic control;

LIV – Large Volume Parenteral Solution (SPGV, in Portuguese): sterile and pyrogenic solution, intended for the parenteral application in a single dose, with a volume of 100mL or more, including solutions for irrigation and solutions for peritoneal dialysis; and

LV – validation: action of proving, in accordance with the principles of Good Manufacturing Practices, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Paragraph 1. The filling of sterile products referred to in item XVIII of the caption of this article is not considered part of the process of packaging operations, with sterile products being considered bulk products when in their primary packaging.

Paragraph 2. Regarding item XXVIII of the caption of this article, for the control of the finished product, a batch of medicinal product includes all units of the pharmaceutical form, which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilization operation or, in the case of a continuous production process, all units manufactured in a given period of time.

CHAPTER II

PHARMACEUTICAL QUALITY SYSTEM

Section I

Introduction

Article 4. The holder of a manufacturing authorization must manufacture medicinal products, in order to ensure they meet their intended purpose, meet the requirements of marketing authorization or authorization for use in a clinical trial, as appropriate, in a way that does not put patients at risk due to inadequate safety, quality, or efficacy.

Paragraph 1. The company's senior management is responsible for the compliance with this quality objective, which requires the participation and commitment of the team at all levels of the organization, as well as of its suppliers and distributors.

Paragraph 2. To reach this quality objective reliably, there must be a comprehensive and correctly implemented Pharmaceutical Quality System, incorporating Good Manufacturing Practices and Quality Risk Management.

Paragraph 3. The Pharmaceutical Quality System must be fully documented and have its effectiveness monitored, through management review, in order to promote continuous quality improvement.

Paragraph 4. All components of the Pharmaceutical Quality System must have adequate resources and competent personnel, in addition to adequate and sufficient facilities and equipment.

Article 5. Quality Management is a comprehensive concept, which covers all issues that determine, either individually or jointly, the quality of a product.

Paragraph 1. The Quality Management corresponds to the sum of the arrangements organized with the objective of guaranteeing that the medicinal products have the required quality for the intended use.

Paragraph 2. Quality Management incorporates Good Manufacturing Practices.

Article 6. The Good Manufacturing Practices apply to all stages of the product life cycle, from the manufacture of experimental medicinal products, technology transfer, commercial manufacturing, up to product discontinuation.

Sole paragraph. The Pharmaceutical Quality System can be extended to the stage of pharmaceutical development, in order to facilitate innovation and continuous improvement, and to strengthen the link between pharmaceutical development and manufacturing activities.

Article 7. The size and complexity of the company's activities must be considered when developing a new Pharmaceutical Quality System or altering an existing one.

Paragraph 1. The system design must incorporate appropriate risk management principles, including the use of appropriate tools.

Paragraph 2. Although some aspects of the system may be corporate of the entire company and others apply to specific establishments, the effectiveness of the system is usually demonstrated at the level of the specific establishment.

Article 8. A Pharmaceutical Quality System suitable for the manufacture of medicinal products must ensure that:

I – the conception of the product is achieved through the design, planning, implementation, maintenance, and continuous improvement of a system that allows consistent manufacture of products with appropriate quality attributes;

II – the knowledge of products and processes is managed at all stages of the life cycle;

III – the medicinal products are designed and developed in such a way as to consider the requirements of Good Manufacturing Practices;

IV – the production and control operations are clearly specified, and the Good Manufacturing Practices are adopted;

V – managerial responsibilities are clearly specified;

VI – arrangements are made for the manufacture, supply, and use of the correct raw materials and packaging materials, the selection and monitoring of suppliers, and verification of the conformity of each receipt with the approved supplier;

VII – there are processes to ensure the management of outsourced activities;

VIII – a state of control is established and maintained through the development and use of effective monitoring and control systems for process performance and product quality;

IX – the results of monitoring of products and processes are considered in the batch release, the investigation of deviations, and with the objective of taking preventive actions to avoid potential deviations that may occur in the future;

X – all necessary controls on intermediate products and any other in-process controls and validations are carried out;

XI – continuous improvement is facilitated through the implementation of quality improvements appropriate to the level of process and product knowledge;

XII – procedures are implemented for the prospective evaluation of planned alterations and their approval prior to implementation, considering regulatory notifications and approvals where necessary;

XIII – after the implementation of any alteration, an evaluation is carried out to confirm that the quality objectives have been achieved and that there has been no unintended harmful impact on the quality of the product;

XIV – an appropriate level of root cause analysis is applied during the investigation of deviations, suspected product defects, and other problems;

XV – the medicinal products are not commercialized or distributed before the Person Delegated by the Pharmaceutical Quality Management System certifies that each batch of the product has been produced and controlled in accordance with the marketing authorization requirements and any other standards relevant to the production, control, and release of medicinal products;

XVI – there are mechanisms to ensure that medicinal products are stored, distributed, and subsequently handled so that quality is maintained throughout its useful life; and

XVII – there is a self-inspection and/ or quality audit process, which regularly evaluates the effectiveness and applicability of the Pharmaceutical Quality System.

Paragraph 1. The appropriate level referred to in item XIV of the caption of this article may be determined by the establishment through the application of Quality Risk Management principles.

Paragraph 2. Regarding item XIV of the caption of this article, in cases where the true root cause(s) of the problem cannot be determined, consideration should be given to identifying the most likely root cause(s) and addressing it (them).

Paragraph 3. Regarding item XIV of the caption of this article, when a human error is suspected or identified as cause, this must be justified, care being taken to ensure that process, procedural, or system errors or problems have not been neglected, accordingly.

Paragraph 4. Regarding item XIV of the caption of this article, appropriate corrective actions and/ or preventive actions (CAPAs) must be identified and implemented in response to investigations, and the effectiveness of such actions must be monitored and evaluated, in accordance with the principles of Quality Risk Management.

Article 9. The company's senior management has the ultimate responsibility for ensuring that an effective Pharmaceutical Quality Management is implemented, adequately resourced, and that responsibilities and authorities are defined, communicated, and implemented throughout the organization.

Paragraph 1. The leadership of the company's senior management and its active participation in the Pharmaceutical Quality System is essential.

Paragraph 2. This leadership must ensure the team’s support and commitment to the Pharmaceutical Quality System at all levels of the organization.

Article 10. There must be regular management review, with the involvement of the company’s senior management, the performance of the Pharmaceutical Quality Management System in order to identify opportunities for continuous improvement of products, processes, and the system itself.

Article 11. The Pharmaceutical Quality System must be defined and documented.

Sole paragraph. A Quality Manual or equivalent documentation must be established and contain a description of the Pharmaceutical Quality Management System, including management responsibilities.

Section II

Good Manufacturing Practices for Medicinal Products

Article 12. Good Manufacturing Practices (GMP) is the part of Quality Management that ensures that products are consistently produced and controlled in accordance with quality standards appropriate for their intended use and required by the marketing authorization, authorization for use in clinical trials, or product specifications.

Paragraph 1. The Good Manufacturing Practices concern both production and quality control.

Paragraph 2. The basic GMP requirements are:

I – all manufacturing processes must be clearly defined, systematically reviewed in the light of experience, and demonstrate that they can produce medicinal products with the required quality and in accordance with their specifications;

II – the critical steps of the manufacturing processes, as well as any significant alterations, must be validated;

III – the provision of all necessary resources, including:

a) qualified and adequately trained personnel;

b) adequate facilities and areas;

c) appropriate equipment and services;

d) correct materials, containers, and labels;

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

f) adequate storage and transportation.

IV – the instructions and procedures must be written in an instructive way, in clear and unambiguous language, specifically applicable to the resources provided;

V – procedures must be followed correctly, and operators must be trained accordingly;

VI – the records, which demonstrate that all the steps required by the defined procedures and instructions have been considered and that the quantity and quality of the product are as expected, must be carried out during manufacturing, manually and/ or through automatic recording instruments;

VII – any significant deviations must be fully recorded and investigated with the objective of determining the root cause and implementing appropriate corrective and preventive actions;

VIII – manufacturing records, including distribution, that allow tracking of the complete history of a batch must be kept in an understandable and accessible form;

IX – the distribution of products must minimize any risk to their quality and consider the good distribution practices;

X – a system must be available to collect any batch of product, either in commercialization or distribution; and

XI – complaints about products must be examined, the causes of quality deviations must be investigated, and appropriate measures must be adopted in relation to products with deviation and in relation to recurrence prevention.

Section III

Quality Control

Article 13. Quality Control is the part of the GMP referring to the collection of samples, the specifications, and the execution of tests, as well as the organization, documentation, and release procedures that ensure the relevant and necessary tests are performed, and that materials are not released for use, or products are not released for commercialization or distribution, until their quality has been considered satisfactory.

Article 14. The basic Quality Control requirements are:

I – adequate facilities, trained personnel, and approved procedures must be available for sampling and testing of raw materials, packaging materials, intermediate products, bulk products, and finished products and, where appropriate, for monitoring environmental conditions for GMP purposes;

II – samples of raw materials, packaging materials, intermediate products, bulk products, and finished products must be collected by authorized personnel using approved methods;

III – the analytical methods must be validated;

IV – (manual or electronic) records must be made, demonstrating that all sampling, inspection, and testing procedures have actually been carried out and that any deviations have been properly recorded and investigated;

V – the finished products must have qualitative and quantitative composition in accordance with what is described in the marketing authorization or authorization for use in clinical trials; the components must have the required purity and be in appropriate and properly labeled containers;

VI – the results of the inspection and tests carried out on materials, intermediate products, bulk products, and finished products must be recorded, demonstrating that they have been formally assessed against the specification, which must include review and assessment of the relevant production documentation and an assessment of deviations from specified procedures;

VII – no product batch must be released for commercialization or distribution before certification, by a Person Delegated by the Pharmaceutical Quality Management System, that it complies with the requirements of the relevant authorizations; and

VIII – sufficient reference samples of raw materials and products must be kept in accordance with the specific normative instruction to allow future analysis of the product, if necessary.

Section IV

Product Quality Review

Article 15. Periodic quality reviews of all authorized medicinal products, including exclusive export products, must be conducted with the objective of verifying the consistency of the existing process, verifying the adequacy of the specifications applied both for raw materials and for the finished product, evidencing any trends, and identifying improvements in products and processes.

Article 16. Product quality reviews should normally be conducted and documented annually, considering previous reviews.

Article 17. The product quality review must include, at least, the review of:

I – raw materials, including the packaging materials used in the product, especially those from new sources and, in particular, the analysis of the traceability of the supply chain of active substances;

II – critical in-process controls and the results of quality control of finished products;

III – all batches that did not comply with the established specifications and their investigations;

IV – all significant deviations or non-conformities, their related investigations, and the effectiveness of the resulting corrective and preventive actions;

V – all alterations made in processes or analytical methods;

VI – submitted, authorized, or rejected post-marketing authorization alterations, including those related to products authorized in other countries (for export only);

VII – the results of the monitoring stability program and any adverse trends;

VIII – all returns, complaints, and collections related to the quality of the product and the investigations carried out at the time;

IX – the adequacy of any previous corrective actions related to the process or product equipment;

X – post-approval commitments for new marketing authorizations and post-marketing authorization alterations;

XI – the qualification status of relevant equipment and utilities, for example, heating, ventilation, and air conditioning (HVAC) system, water, compressed gas systems, among others; and

XII – any contractual provisions, defined in Chapter VIII of this Resolution, referring to outsourced activities to ensure they are up to date.

Article 18. The manufacturer and, eventually, the medicinal product marketing authorization holder, must evaluate the review results and decide whether corrective and preventive action or any revalidation need to be carried out, within the scope of the Pharmaceutical Quality System.

Sole paragraph. Management procedures must be in place for the review and permanent management of the actions referred to in the caption of this article, and the effectiveness of such procedures must be verified during the self-inspection.

Article 19. Quality reviews may be grouped by product type, when scientifically justified.

Article 20. If the marketing authorization holder is not the medicinal product manufacturer, there must be a technical agreement implemented between the parties, which defines the respective responsibilities in the elaboration of the product quality review.

Sole paragraph. The Person Delegated by the Pharmaceutical Quality Management System responsible for the final certification of the batch, together with the marketing authorization holder, must ensure that the quality review is accurate and carried out within the established deadline.

Section V

Quality Risk Management

Article 21. Quality Risk Management (QRM) is a systematic process of assessment, control, communication, and review of risks to the quality of the medicinal product.

Sole paragraph. Quality Risk Management may be applied both proactively and retrospectively.

Article 22. The Quality Risk Management principles are:

I – the quality risk assessment is based on scientific knowledge, experience with the process and, ultimately, is linked to patient protection; and

II – the level of effort, formality, and documentation of the Quality Risk Management process is compatible with the level of risk.

CHAPTER III

PERSONNEL

Section I

Introduction

Article 23. There must be enough qualified personnel to perform correctly all activities for which the manufacturer is responsible.

Article 24. Individual responsibilities must be clearly defined, understood, and recorded by everyone involved.

Article 25. All personnel must be aware of the principles of Good Manufacturing Practices that affect them and receive initial and ongoing training, including hygiene instructions, relevant to their needs.

Section II

General Provisions

Article 26. The manufacturer must have an adequate number of personnel with the necessary qualifications and practical experience.

Article 27. The company's senior management must determine and provide adequate and appropriate resources (human, financial, materials, facilities, and equipment) to implement and maintain the Pharmaceutical Quality System and continuously improve its effectiveness.

Article 28. Responsibilities assigned to any individual should not be so extensive to the point of presenting any risk to quality.

Article 29. The manufacturer must have an organizational chart in which the relationships between the People Responsible for Production, Quality Control and, when applicable, the Person Responsible for Quality Assurance or the Quality Unit, and the position of the Technical Responsible Officer are clearly presented in the management hierarchy.

Article 30. The people who hold responsibility positions must have their specific functions recorded in job descriptions and the appropriate authority to carry out their responsibilities.

Paragraph 1. The responsibility functions may be delegated to designated people with a satisfactory level of qualification.

Paragraph 2. There must be no gaps or unjustified overlaps of responsibility regarding the personnel involved in the application of Good Manufacturing Practices.

Article 31. The company's senior management has the ultimate responsibility for ensuring that an effective Pharmaceutical Quality System is in place to achieve quality objectives, and that roles, responsibilities, and authorities are defined, communicated, and implemented throughout the organization.

Article 32. The company's senior management must establish a quality policy that describes the company's general definitions and intentions in relation to quality and must also ensure the continuous adequacy and effectiveness of the Pharmaceutical Quality System, as well as compliance with the GMP, through participation in management review.

Section III

Key Personnel

Article 33. Senior management must designate Key Management Personnel, including the Production Responsible Officer, the Quality Control Responsible Officer, the Person(s) Delegated by the Pharmaceutical Quality Management System for the release of products.

Sole paragraph. There must be independence between the Production Responsible Officer and the Person(s) Delegated by the Pharmaceutical Quality Management System for the release of products.

Article 34. Key positions should normally be filled by full-time staff.

Article 35. The Production and Quality Control Responsible Officers must be independent from each other.

Paragraph 1. In large organizations, it may be necessary to delegate some of the functions of the Key-Personnel.

Paragraph 2. One person responsible for the Quality Unit or for Quality Assurance may be appointed, depending on the size and organizational structure of the company.

Paragraph 3. When the separation provided for in Paragraph 2 of this article occurs, some of the responsibilities described in Article 36 of this Resolution are shared with the Quality Control Responsible Officer and with the Production Responsible Officer, and the senior management must therefore provide for the definition of roles, responsibilities, and authorities.

Article 36. The Production Responsible Officer has the following responsibilities:

I – ensure that the products are produced and stored in accordance with the appropriate documentation, in order to obtain the required quality;

II – approve the instructions relating to production operations and ensure their strict implementation;

III – ensure that production records are evaluated and signed by a designated person;

IV – ensure the qualification and maintenance of the related department, facilities, and equipment;

V – ensure that the appropriate validations are performed; and

VI – ensure that the initial and continuous training required for the personnel of the related department are carried out and adapted accordingly.

Article 37. The Quality Control Responsible Officer has the following responsibilities, in general:

I – approve or reject, as deemed appropriate, raw materials, packaging materials, intermediate, bulk, and finished products;

II – ensure that all necessary tests are carried out and the associated records are evaluated;

III – approve specifications, sampling instructions, analysis methods, and other Quality Control procedures;

IV – approve and monitor any contracted analysis;

V – ensure the qualification and maintenance of the related department, facilities, and equipment;

VI – ensure that the appropriate validations are carried out; and

VII – ensure that the initial and continuous training of the personnel of the related department are carried out and adapted, accordingly.

Article 38. The officers responsible for Production, Quality Control and, when relevant, the Quality Assurance or Quality Unit Responsible Officer generally have some shared or jointly exercised responsibilities related to quality, including the design, effective implementation, monitoring, and maintenance of the Pharmaceutical Quality System.

Sole paragraph. The responsibilities referred to in the caption of this article may include:

I – the authorization of written procedures and other documents, including amendments;

II – monitoring and control of manufacturing environments;

III – hygiene of the facilities;

IV – process validation;

V – training;

VI – approval and monitoring of material suppliers;

VII – approval and monitoring of contracted manufacturers and providers of other outsourced services related to the GMP;

VIII – establishment and monitoring of storage conditions for materials and products;

IX – retention of records;

X – monitoring the compliance with GMP requirements;

XI – inspection, investigation, and sampling, with the objective of monitoring the factors that may affect the quality of the product;

XII – participation in management reviews of process performance, product quality, and the Pharmaceutical Quality System in search of continuous improvement; and

XIII – ensuring that there is a communication process as well as a temporal and effective scheduling of so that quality issues are addressed at the appropriate levels of management.

Section IV

Training

Article 39. The manufacturer must provide training for all personnel whose duties are performed in the areas of production and storage or control laboratories (including technical, maintenance, and cleaning personnel), and for other people whose activities may affect the quality of the product.

Article 40. In addition to basic training on the theory and practice of the Pharmaceutical Quality System and GMP, newly hired personnel must receive adequate training for the tasks assigned to them.

Article 41. Ongoing training must be provided, and its practical effectiveness must be periodically evaluated.

Article 42. Training programs must be available, approved by the Production Responsible Officer or by the Quality Control Officer, as appropriate.

Article 43. Training records must be maintained.

Article 44. Personnel working in areas at risk of microbiological contamination of products, for example in clean areas, or personnel working in areas at risk of operator contamination and cross-contamination of products, such as areas where highly active, toxic, infectious, or sensitizing materials are handled, must receive specific training.

Article 45. Visitors or untrained personnel should preferably not be driven by the areas of production and quality control.

Sole paragraph. If it is unavoidable, they should be carefully supervised and given information in advance, especially about personal hygiene and necessary protective clothing.

Article 46. The Pharmaceutical Quality System and all measures capable of improving its understanding and implementation must be extensively discussed during training sessions.

Section V

Personal Hygiene and Health

Article 47. Detailed hygiene programs must be established and adapted to the various needs of the plant.

Article 48. Hygiene programs must include health-related procedures, hygiene practices, and attire.

Sole paragraph. These procedures must be understood and strictly followed by all the people whose functions imply their presence in the areas of production and control.

Article 49. Management must promote hygiene programs which must be widely discussed during training sessions.

Article 50. All personnel must undergo a medical examination at the time of employment.

Article 51. After the first medical examination, other tests must be carried out when necessary to ensure work and personal health.

Article 52. The manufacturer is responsible for providing written instructions to ensure that the health conditions of its employees that may impact the quality of the products are immediately informed.

Article 53. Measures must be taken to ensure that no person affected by an infectious disease or who has open lesions on the exposed surface of the body is involved in the manufacture of medicinal products.

Article 54. Everyone entering manufacturing areas must wear protective clothing adequate to the operations to be performed.

Article 55. Eating, drinking, chewing, smoking, or storing food, beverages, materials derived from tobacco, or medicinal products for personal use in production and storage areas is prohibited.

Article 56. Any practice that is not hygienic within manufacturing areas or in any another area where the product could be adversely affected must be prohibited.

Article 57. Direct contact between the operator's hands and the exposed product, as well as any part of the equipment that comes into contact with the products, must be avoided.

Article 58. Staff must be instructed on the use of hand washing facilities.

Article 59. Any specific requirements for the manufacture of special groups of products, for example, sterile preparations, are set out in specific normative instructions.

Section VI

Consultants

Article 60. Consultants must have adequate education, training, and experience so they are capable of advising on the subject for which they were selected.

Article 61. Records must be kept with information on name, address, qualifications, and type of service provided by consultants.

CHAPTER IV

FACILITIES AND EQUIPMENT

Section I

Introduction

Article 62. Facilities and equipment must be located, designed, constructed, adapted, and maintained in accordance with the operations to be performed.

Article 63. The design and the project must minimize the risk of errors and allow for effective cleaning and maintenance, in order to avoid cross-contamination, accumulation of dust or dirt, or any damage to the quality of the products.

Section II

Installations

Subsection I

General Provisions

Article 64. Facilities must be located in a place that, when considered together with measures to protect the manufacturing process, presents minimal risk of causing any contamination of materials or products.

Article 65. Facilities must be carefully maintained, ensuring that repair and maintenance operations do not present any risk to the quality of the products.

Article 66. Facilities must be cleaned and, where appropriate, disinfected in accordance with detailed written procedures.

Article 67. Lighting, temperature, humidity, and ventilation must be adequate and must not harm, either directly or indirectly, the medicinal products during their manufacture and storage, or the precise functioning of the equipment.

Article 68. Facilities must be designed and equipped to ensure maximum protection against the entry of insects or other animals.

Article 69. Measures must be taken to prevent unauthorized people from entering the facilities in general.

Article 70. Production, storage, and quality control areas must not be used as passage by personnel who do not work in such areas.

Subsection II

Production Areas

Article 71. Cross-contamination must be prevented for all products through proper design and proper operation of manufacturing facilities.

Paragraph 1. The measures to prevent cross-contamination must be proportionate to the risks.

Paragraph 2. The principles of Quality Risk Management must be used to assess and control the risks.

Paragraph 3. Depending on the level of risk, it may be necessary to dedicate facilities and equipment to manufacturing and/ or packaging operations in order to control the risk posed by some medicinal products.

Paragraph 4. Dedicated facilities are required for manufacturing when:

I – the risk cannot be adequately controlled by operational and/ or technical measures;

II – the scientific data of the toxicological evaluation do not support a controllable risk, such as the allergenic potential of highly sensitizing materials, including beta-lactams; and

III – the relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

Article 72. Facilities should preferably be planned in a way that allows production is carried out in interconnected areas according to a logical order, which corresponds to the sequence of operations and the required cleaning levels.

Article 73. The workspace and the storage area during processing must allow for the orderly and logical arrangement of equipment and materials, in order to minimize the risk of mixing among different pharmaceutical products or their components, avoid cross-contamination, and minimize the risk of omission or incorrect application of any of the manufacturing or control stages.

Article 74. In areas where raw materials, primary packaging materials, intermediate products, or bulk products are exposed to the environment, the internal surfaces (walls, floors, and ceilings) must be smooth, free of cracks and open joints, and must not release particulate material, allowing for easy and effective cleaning and, if necessary, disinfection.

Article 75. Pipes, luminaires, ventilation points, and other installations must be designed and installed in such a way as to avoid the creation of recesses and facilitate cleaning.

Article 76. Whenever possible, the access for maintenance should be located outside of the manufacturing areas.

Article 77. Drains must be siphoned and of adequate dimensions.

Article 78. Open channels should be avoided; however, if necessary, these should be shallow to facilitate cleaning and disinfection.

Article 79. Production areas must be effectively ventilated, with air treatment installations, including temperature and, where necessary, humidity and filtration installations, appropriate to the products handled, the operations carried out, and the external environment.

Article 80. The weighing of raw materials should usually be carried out in a separate room, designed for such use.

Article 81. In cases where dust is generated, such as during sampling, weighing, mixing, and processing operations, or during the packaging of solid products, specific measures must be taken to avoid cross-contamination and facilitate cleaning.

Article 82. The packaging facilities for medicinal products must be specifically designed and constructed so that mixing or cross-contamination is avoided.

Article 83. Production areas must be well lit, particularly where in-line visual controls are carried out.

Article 84. In-process controls may be performed in the production area, as long as they do not pose risks to such activity.

Subsection III

Storage Areas

Article 85. Storage areas must have sufficient capacity to allow orderly storage of the various categories of materials and products, such as raw materials, packaging materials, intermediate, bulk, and finished products, in their quarantine, released, rejected, returned, or collected conditions.

Article 86. Storage areas must be designed or adapted to ensure ideal storage conditions, and must be clean, dry, and kept within acceptable temperature limits.

Sole paragraph. In cases where special storage conditions are required, such as temperature and humidity, these must be provided, verified, and monitored.

Article 87. Receiving and shipping areas must protect materials and products from climatic variations.

Article 88. Receiving areas must be designed and equipped to allow containers to be cleaned, if necessary, before storage.

Article 89. If quarantine is ensured through storage in separate areas, these areas must be clearly identified and the access to them must be restricted to authorized personnel.

Sole paragraph. Any system that replaces physical quarantine must provide an equivalent degree of security.

Article 90. Preferably, there should be a separate area for the sampling of raw materials.

Sole paragraph. If sampling is carried out in the storage area, it must be conducted in such a way as to avoid contamination or cross-contamination.

Article 91. There must be segregated places for the storage of materials or rejected, recalled, or returned products.

Article 92. Highly active materials or products must be stored in secure and protected areas.

Article 93. Secure storage of printed packaging materials, as well as other materials considered critical for the conformity of medicinal products, must be ensured.

Subsection IV

Quality Control Areas

Article 94. Quality Control laboratories should preferably be separated from production areas.

Sole paragraph. The control laboratories for biological products, microbiological products, and radioisotopes must also be separated not only from each other, but also from the production areas.

Article 95. Control laboratories must be designed for the operations performed.

Sole paragraph. There must be sufficient space to avoid mixing and cross-contamination, as well as for the proper storage of samples and records.

Article 96. Separate rooms may be necessary to protect instruments sensitive to vibration, electrical interference, moisture, etc.

Article 97. Special requirements are necessary in laboratories that handle certain substances, such as biological or radioactive samples.

Subsection V

Auxiliary Areas

Article 98. Lounge rooms and refectories must be separated from other areas.

Article 99. Changing rooms and toilets must be easily accessible and appropriate for the number of users.

Article 100. Toilets must not communicate directly with production or storage areas.

Article 101. Maintenance areas must be located in separate places from the production areas.

Sole paragraph. If parts and tools need to be stored in the production area, these must be kept in rooms or cabinets reserved for such purpose.

Article 102. Animal facilities must be isolated from other areas, have a separate entrance for animals, and an exclusive ventilation system.

Section III

Equipment

Article 103. Equipment used in manufacturing must be designed, located, and maintained in accordance with the intended purpose.

Article 104. Repair and maintenance operations must not present any danger to product quality.

Article 105. Manufacturing equipment must be designed in a way to allow for easy and complete cleaning.

Sole paragraph. Manufacturing equipment must be cleaned in accordance with written detailed procedures and must be stored only if they are clean and dry.

Article 106. Washing and cleaning of equipment must be selected and carried out in a way that they do not constitute a source of contamination.

Article 107. Equipment must be installed in such a way as to avoid any risk of error or contamination.

Article 108. Production equipment must not present any danger to products.

Sole paragraph. The parts of such equipment that come into contact with the products must not be reactive, additive, or absorptive to such an extent that they affect the quality of the product and therefore represent danger.

Article 109. Scales and measuring equipment, with appropriate accuracy and scale, must be available for production and control operations.

Article 110. Measuring, weighing, recording, and control equipment must be calibrated and checked at defined intervals and through appropriate methods.

Sole paragraph. Adequate records of the calibration referred to in the caption of this article must be kept.

Article 111. Fixed piping must be clearly identified to indicate its content and, when applicable, the flow direction.

Article 112. Piping of purified water and water for injection and, if applicable, any other type of water, must be sanitized according to written procedures that contain details on the limits of microbiological contamination, as well as the measures to be adopted.

Article 113. Defective equipment should, if possible, be removed from production and quality control areas or, when removal is not possible, it should at least be clearly identified as such.

CHAPTER V

DOCUMENTATION

Section I

Introduction

Article 114. Documentation is an essential part of the Pharmaceutical Quality Management System, being critical to operate in accordance with the requirements of Good Manufacturing Practices.

Paragraph 1. The various types of documents and media used must be fully defined in the manufacturer's Pharmaceutical Quality Management System.

Paragraph 2. Documentation may exist in a variety of forms, including printed, electronic, or photographic media.

Paragraph 3. The main objective of the documentation system used must be to establish, control, monitor, and record all activities that directly or indirectly affect all aspects of the quality of medicinal products.

Paragraph 4. The documentation that constitutes the Pharmaceutical Quality Management System must include sufficient instructive information to facilitate a common understanding of the requirements and allow for the satisfactory recording of the various processes and the assessment of any observations, so that continued application of the requirements may be demonstrated.

Article 115. There are two main types of documentation used to manage and record the compliance with Good Manufacturing Practices, instructions (guidelines and requirements), and records and/ or reports.

Sole paragraph. Good Documentation Practices must be applied according to the type of document.

Article 116. Adequate controls must be implemented to ensure the accuracy, integrity, availability, and readability of documents.

Paragraph 1. The instruction documents must be free from errors and available in writing.

Paragraph 2. The term "in writing" means recorded or documented in media from which the data may be processed in a human-readable format.

Section II

Generation and Control of Documentation

Article 117. All types of documents must be defined and complied with.

Paragraph 1. The requirements must be equally applied to all types of document media.

Paragraph 2. Complex systems need to be understood, well documented, validated, and adequate controls must be in place.

Paragraph 3. The documents (instructions and records) may exist in a hybrid form, having electronic and paper elements.

Paragraph 4. Control and relationship measures for master documents, official copies, handling of data and records need to be defined for hybrid and homogeneous systems.

Paragraph 5. Appropriate controls must be implemented for electronic documents, such as templates, forms, and master documents.

Paragraph 6. During the entire retention period, there must be appropriate controls in place to guarantee record integrity.

Article 118. Documents must be designed, prepared, reviewed, and distributed with caution.

Paragraph 1. The documents must comply with the relevant parts of the files of product specification, manufacturing, and marketing authorization dossiers, as appropriate.

Paragraph 2. The reproduction of working documents from master documents must not allow errors to occur.

Article 119. Documents containing instructions must be approved, signed, and dated by appropriate and authorized people.

Paragraph 1. The documents must have unambiguous content and unique identification.

Paragraph 2. The effective date of the documents must be defined.

Article 120. Documents containing instructions must be arranged in an orderly way of easy verification.

Paragraph 1. The style and language of the documents must suit the intended use.

Paragraph 2. The Standard Operating Procedures, Work Instructions, and Methods must be preferably written in the imperative mode.

Article 121. Documents related to the Pharmaceutical Quality Management System must be regularly reviewed and kept up to date.

Sole paragraph. When a document is reviewed, the systems must operate in a way to prevent the inadvertent use of obsolete documents.

Article 122. Documents must not be handwritten.

Sole paragraph. In cases where there is a need to enter data, there must be enough space for such inserts.

Section III

Good Documentation Practices

Article 123. Handwritten entries must be made in a clear, legible, and indelible manner.

Article 124. Records must be carried out or completed whenever an action is performed and in such a way to allow the traceability of all significant medicinal product manufacturing activities.

Article 125. Any alteration made to a document record must be signed and dated, and it must allow the original information to be read.

Sole paragraph. Where appropriate, the reason for the alteration should be recorded.

Section IV

Document Retention

Article 126. It must be clearly defined which record each manufacturing activity is related to and where such record is located.

Sole paragraph. There must be safe and, if necessary, validated controls, in order to guarantee the integrity of the record throughout the retention period.

Article 127. The batch documentation must be kept for one year after the expiration of the batch to which it refers or for at least five years, after batch certification by a Person Delegated by the Pharmaceutical Quality Management System, whichever is longer.

Paragraph 1. In the case of experimental medicinal products, the batch documentation must be kept for at least five years after completion or formal discontinuation of the last clinical trial in which the batch was used.

Paragraph 2. Other requirements for the retention of documentation may be described in the legislation regarding specific product types (for example, Advanced Therapy Medicinal Products) and may specify the need for longer retention periods for certain documents.

Article 128. The retention period for other types of documents must be defined according to their supporting purpose.

Paragraph 1. The critical documentation, including raw data (for example, related to validation or stability), which supports marketing authorization information, must be maintained as long as the authorization remains in effect.

Paragraph 2. The obsolescence and subsequent non-retention of data, such as validation and stability studies, which have been superseded by a complete set of new data, is acceptable provided that the documentation does not have a temporal retention time determination in effect by virtue of being related to a commercial batch.

Section V

Specifications

Article 129. There must be duly authorized and dated specifications for raw materials, packaging materials, and finished products.

Subsection I

Specifications for Raw Materials and Packaging Materials

Article 130. Specifications of raw materials and primary packaging materials or printed materials must include or refer to the following items, if applicable:

I – description of materials, including:

a) the name and reference of the internal code;

b) the reference, if any, to a pharmacopoeial monograph;

c) the approved suppliers and, where relevant, the original manufacturer of the material; and

d) a model or artwork of the printed materials.

II – instructions for sampling and analysis;

III – qualitative and quantitative requirements with acceptance limits;

IV – storage conditions and precautions; and

V – the maximum storage period before a reanalysis.

Subsection II

Specifications for Intermediate and Bulk Products

Article 131. Specifications for intermediate and bulk products must be available for critical stages or if these products are purchased or shipped.

Sole paragraph. These specifications must be similar to the specifications for raw materials or for finished products, accordingly.

Subsection III

Specifications for Finished Products

Article 132. Specifications for finished products must include or refer to:

I – product name and reference code, when applicable;

II – formula;

III – description of the pharmaceutical form and packaging details;

IV – instructions for sampling and analysis;

V – qualitative and quantitative requirements, with acceptance limits;

VI – storage conditions and any special handling precautions, when applicable; and

VII – validity period.

Section VI

Manufacturing Formula and Process Instructions

Article 133. There must be approved and written manufacturing formulas and process instructions for each product and batch size to be manufactured.

Article 134. The manufacturing formula must include:

I – name and reference code of the product related to its specification;

II – description of the pharmaceutical form, product concentration, and batch size;

III – list of all raw materials to be used, with the described quantity of each one, with the reference to any substance that may disappear during the process; and

IV – statement of expected final yield with acceptable limits and relevant yield of intermediate products, where applicable.

Article 135. Process instructions must include:

I – statement of the process location and the main equipment to be used;

II – the methods, or reference to the methods, to be used to prepare critical equipment (for example, cleaning, assembly, calibration, sterilization);

III – checks to confirm that the equipment and the workstation are free of previous products, documents, or materials not necessary for the planned process, and that the equipment is clean and suitable for use;

IV – detailed process instructions per stage [for example, checks of materials, pretreatments, sequence of addition of materials, and critical process parameters (time, temperature, etc.);

V – the instructions for any in-process control and its limits;

VI – when necessary, the requirements for the storage of bulk products; including the container, labeling, and special storage conditions, when applicable; and

VII – any special precautions to be observed.

Subsection I

Packaging Instructions

Article 136. There must be approved instructions for the packaging operation of each product, size, and type of packaging.

Sole paragraph. The instructions referred to in the caption of this article must include, or refer to:

I – name of the product, including the batch number of the bulk and finished product;

II – description of its pharmaceutical form and concentration, when applicable;

III – package size expressed in number, weight, or volume of the product in the final container;

IV – a complete list of all necessary packaging materials, including quantities, sizes, and types, with the code or reference number relating to the specifications of each packaging material;

V – where appropriate, an example or reproduction of relevant printed packaging materials and instructions indicating where to apply the references to the batch numbers and validity period of the product;

VI – checks to confirm that the equipment and the workstation are free of previous products, documents or materials not necessary for the planned packaging operations (line release), and that the equipment is clean and suitable for use;

VII – special precautions to be observed, including a careful examination of the area and the equipment, in order to ensure the release of the line before the start of operations;

VIII – a description of the packaging operation, including any significant subsidiary operations, and the equipment to be used; and

IX – details of the in-process controls with instructions for sampling and acceptance limits.

Subsection II

Batch Processing Record

Article 137. A batch processing record must be kept for each batch processed.

Paragraph 1. This record must be based on the relevant parts of the Manufacturing Formula and the Process Instructions currently approved, and must contain the following information:

I – name and batch number of the product;

II – dates and times of the start of significant intermediate stages and of production completion;

III – identification (initials) of the operator(s) who performed each significant stage of the process and, where appropriate, the name of any person who verified such operations;

IV – batch number and/ or analytical control number, as well as the quantities of each raw material effectively weighed, including the batch number and the quantity of any recovered or reprocessed material added;

V – any relevant manufacturing operation or event and the main equipment used;

VI – record of the in-process controls and the initials of the person(s) who performed them and the results obtained;

VII – yield obtained from the product in different and relevant manufacturing stages;

VIII – remarks on any problems including the details, with signed authorization for any deviation from the Manufacturing Formula and Process Instructions; and

IX – approval of the manufacturing operations by the person responsible for it.

Paragraph 2. In the case of validated, continuously controlled and monitored processes, the reports generated automatically may be limited to compliance summaries and out-of-specification exception/ outcome data reports.

Subsection III

Batch Packing Record

Article 138. A batch packaging record must be kept for each batch or part of batch processed.

Sole paragraph. This record must be based on the relevant parts of the Packaging Instructions.

Article 139. The batch packaging record must contain the following information:

I – name and batch number of the product;

II – date(s) and times of packaging operations;

III – identification (initials) of the operator(s) who performed each significant stage of the process and, where appropriate, the name of any person who verified such operations;

IV – records of the verifications of identity and compliance with the Packaging Instructions, including the results of in-process controls;

V – details of the packaging operations carried out, including references to equipment and packaging lines used;

VI – whenever possible, samples of printed packaging materials used, including examples of batch coding, expiration date, and any additional overprints;

VII – remarks on any problems or unusual events, including details, with signed authorization for any deviation from the Packaging Instructions;

VIII – quantities and reference or identification number of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained, in order to provide an adequate reconciliation, with the possibility of justification for not including this information, in case there are robust electronic controls implemented during packaging; and

IX – approval by the person responsible for the packaging operations.

Section VII

Procedures and Records

Subsection I

Receipt

Article 140. There must be written procedures and records for the receipt of each delivery of raw material (including bulk, intermediate, or finished products), primary, secondary, and printed packaging materials.

Article 141. Receipt records must include:

I – the name of the material and the number of recipients on the delivery note;

II – the name and/ or internal code of the material, if different from the corresponding information referred to in item I of this article;

III – the date of receipt;

IV – the name of the supplier and the name of the manufacturer;

V – the manufacturer's batch number or reference number;

VI – the total quantity and number of recipients received;

VII – the batch number assigned after receipt; and

VIII – any relevant comment.

Article 142. There must be written procedures regarding internal labelling, quarantine, and storage of raw materials, packaging materials, and other materials, as appropriate.

Subsection II

Sampling

Article 143. There must be written procedures for sampling, which include the methods and equipment to be used, the quantities to be sampled, and any precautions to be observed to avoid contamination of the material or any deterioration of its quality.

Subsection III

Analysis

Article 144. There must be written procedures to analyze materials and products in different manufacturing stages, describing the methods and equipment to be used.

Article 145. The tests performed must be recorded.

Subsection IV

Others

Article 146. Written clearance and rejection procedures must be available for materials and products and particularly for the certification of the finished product for sale by the Person Delegated by the Pharmaceutical Quality Management System.

Paragraph 1. All records must be available to the Person Delegated by the Pharmaceutical Quality Management System.

Paragraph 2. A system must be in place to indicate special observations and any alterations in critical data.

Article 147. Records must be kept for the distribution of each batch of a product in order to facilitate collection, if necessary.

Article 148. There must be policies, procedures, protocols, reports, and records of actions taken or conclusions reached, where appropriate, for the following examples:

I – validation and qualification of processes, equipment, and systems;

II – assembly and calibration of equipment;

III – technology transfer;

IV – maintenance, cleaning, and sanitization;

V – personnel issues, including subscription lists, training in Good Manufacturing Practices and technical topics, clothing and hygiene, and verification of training effectiveness;

VI – environmental monitoring;

VII – pest control;

VIII – complaints;

IX – collection;

X – returns;

XI – alteration control;

XII – investigations into deviations and non-conformities;

XIII – internal audits of quality and Good Manufacturing Practices;

XIV – record summaries, when appropriate (for example, product quality review); and

XV – audits of suppliers.

Article 149. Clear operating procedures must be available for the main manufacturing and testing equipment.

Article 150. Record books must be kept for important or critical analytical tests, production equipment, and areas where the product was processed.

Sole paragraph. The record books must 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 identification of people who carried out such operations.

Article 151. An inventory of documents must be maintained within the Pharmaceutical Quality Management System.

CHAPTER VI

PRODUCTION

Section I

Introduction

Article 152. Production operations must observe clearly defined procedures, must satisfy the principles of Good Manufacturing Practices in order to obtain products with the required quality and in compliance with the respective manufacturing authorizations and marketing authorization.

Section II

General Provisions

Article 153. Production must be carried out and supervised by competent people.

Article 154. All material and product handling, such as receiving and quarantining, sampling, storage, labeling, dispensing, processing, packaging, and distribution must be done in accordance with written procedures or instructions and, if necessary, be recorded.

Article 155. All incoming materials must be verified to ensure that the shipment matches the order.

Sole paragraph. Containers must be cleaned whenever needed and labeled in a way that they include the data required by the receiving company's quality system.

Article 156. Damages to containers and any other problem that could adversely affect the material quality must be investigated, recorded, and reported to the Quality Unit.

Article 157. Incoming materials and finished products must be physically or administratively quarantined immediately upon receipt or processing, until they are released for use or distribution.

Article 158. Intermediate and bulk products, purchased as such, must be handled at receipt as if they were raw materials.

Article 159. All materials and products must be stored under appropriate conditions, defined by the manufacturer in order to enable the segregation of batches and stock rotation.

Article 160. Yield checks and reconciliation of quantities must be carried out whenever necessary to ensure that there are no discrepancies outside the acceptable limits.

Article 161. Operations involving different products must not be carried out simultaneously or consecutively in the same room, unless there is no risk of mixing or cross-contamination.

Article 162. At all stages of the process, materials and products must be protected against microbial contamination and other types of contamination.

Article 163. Special precautions must be taken when working with dry materials or products, in order to avoid the generation and spread of dust.

Sole paragraph. The determination referred to in the caption of this article applies particularly to the handling of highly hazardous materials, including highly sensitizing materials.

Article 164. At all times during the process, all materials, bulk containers, main items of equipment and, where necessary, the rooms used must be labeled and identified with an indication of the product or material being processed, its concentration, where applicable, and batch number.

Sole paragraph. When applicable, the indication referred to in the caption of this article must also mention the stage of production.

Article 165. Labels applied to containers, equipment, or facilities must be clear, unambiguous, and in the format agreed by the company.

Sole paragraph. It is recommended and useful that, in addition to the text on the labels, colors are used to indicate the status (for example, quarantined, approved, rejected, clean).

Article 166. Verifications must be carried out to ensure that ducts and other parts of equipment used to transport materials and products from one area to another are properly connected.

Article 167. Any deviation from instructions or procedures must be avoided.

Sole paragraph. If a deviation occurs, it must be formally approved by a competent person, with the involvement of the Quality Unit, when appropriate.

Article 168. Access to production facilities must be restricted to authorized personnel.

Section III

Prevention of Cross-Contamination in Production

Article 169. The manufacture of non-medicinal products should be avoided in areas and equipment intended for the production of medicines, however, as long as it is justified, it may be authorized provided that the measures to prevent cross-contamination described in this Section and in Chapter IV of this Resolution are applied.

Sole paragraph. The production and/ or storage of agrochemicals, such as pesticides (except when used for the manufacture of medicines) and herbicides, cannot be authorized in areas used for the manufacture and/or storage of medicinal products.

Article 170. Contamination of a raw material or a product by another raw material or product must be avoided.

Paragraph 1. The risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapors, aerosols, genetic material or organisms from active substances, other (starting or in-process) materials and in-process products, waste on equipment, and operators' clothing must be assessed.

Paragraph 2. The significance of such risk varies with the nature of the contaminant and that of the product that is being contaminated.

Paragraph 3. Cross-contamination is probably the most significant in products administered by injection or for a long period of time.

Paragraph 4. The contamination of all products represents a risk to patient safety, depending on the nature and extent of the contamination.

Article 171. Cross-contamination must be avoided through attention to the design of facilities and equipment, as described in Chapter IV of this Resolution.

Sole paragraph. The prevention of cross-contamination must include attention to the design of the process and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes, with a view to controlling the risk of cross-contamination.

Article 172. A Quality Risk Management process, which includes toxicological and potency assessment, must be used to assess and control the risks of cross-contamination presented by manufactured products.

Paragraph 1. Factors including the design and use of the facility/ equipment, personnel and material flow, microbiological controls, physical-chemical characteristics of the active substance, process characteristics, cleaning processes, and analytical capabilities referring to the relative limits established from the evaluation of the products must also be considered.

Paragraph 2. The result of the Quality Risk Management process must be the basis to determine the need and extent of which facilities and equipment must be dedicated to a particular product or product family.

Paragraph 3. The result may include the dedication of specific parts of contact with the product or the dedication of the entire manufacturing facility.

Paragraph 4. It may be acceptable to restrict manufacturing activities to a production area segregated and self-contained within a multi-product facility when the need arises.

Article 173. The outcome of the Quality Risk Management process must be the basis to determine the extent of technical and organizational measures necessary to control the risks of cross-contamination.

Sole paragraph. The technical and organizational measures referred to in the caption of this article may include, but are not limited to, the following:

I – technical measures:

a) dedicated manufacturing facility (facilities and equipment);

b) self-contained production areas with production equipment and separate heating, ventilation, and air conditioning systems, and it is desirable to isolate certain utilities from others used in other areas;

c) design of the manufacturing process, facilities, and equipment to minimize the risk of cross-contamination during process, maintenance, and cleaning;

d) use of "closed systems" for production and material/ product transfer between pieces of equipment;

e) use of physical barrier systems, including isolators, as containment measures;

f) controlled dust removal close to the source of the contaminant, for example by means of localized exhaustion;

g) dedication of equipment, parts that come into contact with the product, or selected parts that are more difficult to clean (for example, filters), and dedication of maintenance tools;

h) utilization of technology of single-use disposables;

i) use of equipment designed to facilitate cleaning;

j) appropriate use of antechambers and pressure cascade to confine a potential airborne contaminant in a specific area;

k) minimization of the risk of contamination caused by the recirculation or re-entry of air not treated or insufficiently treated;

l) use of (clean in place) local automatic cleaning systems of validated effectiveness; and

m) for common washing areas, separation of washing, drying, and equipment storage areas.

II – organizational measures:

a) dedication of the entire production facility or the use of a self-contained production area in a campaign organized by time, followed by a cleaning process of validated effectiveness;

b) maintenance of specific protective clothing within areas where products of high cross-contamination risk are processed;

c) cleaning verification after each product campaign should be considered as a detection tool to support the effectiveness of the Quality Risk Management approach for products deemed to be of greatest risk;

d) cleaning verification of surfaces that have not had contact with the product and monitoring of the air within the manufacturing area and/ or adjacent areas, depending on the risk of

contamination, in order to demonstrate the effectiveness of control measures for air contamination or contamination through mechanical transfer;

e) specific measures for the handling of waste, contaminated rinse water, and dirty clothes;

f) record of spills, accidental events, or deviations from procedures;

g) design of cleaning processes for facilities and equipment, in such a way that the cleaning processes themselves do not pose a risk of cross-contamination;

h) detailed instructions for cleaning process records to ensure completion of the cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;

i) use of common washing areas in a campaign; and

j) supervision of on-the-job behavior to ensure the effectiveness of training and the compliance with relevant in-process controls.

Article 174. Measures to prevent cross-contamination and their effectiveness must be reviewed periodically in accordance with the procedures established.

Section IV

Validation

Article 175. Validation studies must reinforce Good Manufacturing Practices and be conducted in accordance with defined procedures.

Sole paragraph. The results and conclusions from validation studies must be recorded.

Article 176. When any new manufacturing formula or method of preparation is adopted, measures must be taken to demonstrate its suitability to the routine process.

Sole paragraph. The defined process referred to in the caption of this article, which uses the materials and equipment established, must demonstrate that it manufactures the product with the required quality on a consistent basis.

Article 177. Significant alterations in the manufacturing process, including any alteration in equipment or materials, which may affect product quality and/ or process reproducibility, must be validated.

Article 178. Processes and procedures may undergo periodic critical revalidation with the purpose of ensuring that they remain capable of achieving the intended results.

Section V

Raw Materials

Article 179. The selection, qualification, approval, and maintenance of raw material suppliers, along with their purchasing and acceptance process, must be documented as part of the Pharmaceutical Quality Management System.

Paragraph 1. The level of supervision of the activities referred to in the caption of this article must be proportional to the risks posed by individual materials, considering their origin, the manufacturing process, the complexity of the supply chain, and the end use to which the material is put in the medicinal product.

Paragraph 2. Evidence of the approval of each supplier/ material must be available.

Paragraph 3. The team involved in the activities referred to in the caption of this article must have an updated knowledge about the suppliers, the supply chain, and the associated risks.

Paragraph 4. Whenever possible, the raw materials must be purchased directly from their manufacturer.

Article 180. The quality requirements established by the manufacturer for raw materials must be discussed and agreed with suppliers.

Sole paragraph. Appropriate aspects of production, testing, and control, including requirements for handling, labeling, packaging, and distribution procedures, complaints, recall, and rejection, must be documented as part of a formal quality or specification agreement.

Article 181. For the approval and maintenance of active pharmaceutical ingredients, the following items are required:

I – the traceability of the supply chain must be established, and the associated risks must be formally assessed and verified on a regular basis, from the raw materials to the finished medicinal product, and adequate measures must be taken to reduce the risks to the quality of the active pharmaceutical ingredient;

II – the records of the supply chain and of the traceability of each pharmaceutical ingredient active, including its starting materials, must be maintained and fully available from the manufacturer of the medicinal product;

III – the audits must be carried out on the manufacturers and distributors of active pharmaceutical ingredients in order to confirm that they are complying with the good manufacturing practices and the requirements of good distribution practices;

IV – the audits referred to in item III of the caption of this article may be carried out by the company itself or through an entity acting on its behalf, in the terms of a contract;

V – the audits must have adequate duration and scope to ensure a complete and clear assessment of the Good Manufacturing Practices, with special attention to the potential for cross-contamination of other materials on site;

VI – the report must fully reflect what was done and seen in the audit, any deficiencies must be clearly identified, and the necessary corrective and preventive actions must be implemented; and

VII – subsequent audits must be carried out at intervals defined by the Quality Risk Management process, to ensure maintenance of standards and ongoing use of the approved supply chain.

Article 182. Excipients and their suppliers must be properly controlled based on the results of a formalized quality risk assessment.

Article 183. For each delivery of raw material, containers must be checked for packaging integrity, including the violation evidence seal where applicable; correspondence between the delivery

note, the purchase order, the supplier labels, and the information approved by the manufacturer of the medicinal product for the manufacturer and supplier of the excipients must also be verified.

Sole paragraph. The verifications upon receipt of each delivery must be documented.

Article 184. If a material delivery is comprised of different batches, each batch must be considered separately for sampling, analysis, and release.

Article 185. Raw materials in the storage area must be properly labeled.

Sole paragraph. The labels must contain at least the following information:

I – product name and internal code reference, when applicable;

II – batch number given upon receipt;

III – status of the content (for example, quarantined, under analysis, approved, rejected), when applicable; and

IV – expiration date or retest date, indicating the need for a new test, when applicable.

Article 186. When fully computerized storage systems are used, the information referred to in Article 185 of this Resolution do not necessarily need to be in written form on the label.

Article 187. There must be appropriate procedures or measures in place to ensure the identity of the contents of each raw material container.

Article 188. The containers from which samples were taken for the identity test must be identified.

Article 189. Only raw materials that have been released by the Quality Control department and that are within their retest date must be used.

Article 190. Finished product manufacturers are responsible for any testing of raw materials as described in the marketing authorization dossier.

Sole paragraph. Partial or total results from the approved raw material manufacturer may be used, however, in each batch, at least the identification test must be carried out.

Article 191. When using partial or total results from the raw material manufacturer approved in the analysis certificate of the finished product manufacturer, the following items must be evaluated:

I – special attention must be given to the control of the distribution chain, in its stages of transportation, distribution, storage, and receipt, in order to maintain the quality characteristics of the raw materials and ensure that the test results remain applicable to the material delivered;

II – the medicinal product manufacturer must carry out audits on its own account or through third parties, at appropriate intervals, based on the risk of the raw material testing (including sampling) site(s), in order to ensure compliance with the Good Manufacturing Practices and the specifications and methods of analysis described in the marketing authorization dossier;

III – the certificate of analysis provided by the raw material manufacturer/ supplier must be signed by a designated person with appropriate qualifications and experience, ensuring that

each batch has been verified for compliance with the agreed product specification, unless such assurance is provided separately;

IV – the medicinal product manufacturer must have adequate experience in dealing with the raw material manufacturer (including experience with possible intermediaries), which includes the evaluation of previously received batches and the history of conformity before reducing internal testing, and any significant alteration in manufacturing or testing processes must be considered; and

V – the medicinal product manufacturer must also carry out a complete analysis (at its own expense or through a contractually approved laboratory) at appropriate intervals, based on risk, and compare the results with the manufacturer's or supplier's certificate of analysis to verify its reliability.

Sole paragraph. If the comparison referred to in item V of the caption of this article identifies any discrepancy, an investigation must be carried out, appropriate measures must be taken, and acceptance of certificates of analysis from the material manufacturer or supplier must be discontinued until such measures are completed.

Article 192. Raw materials may only be weighed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured in clean, properly labeled containers.

Article 193. Each material weighed and its weight or volume must be verified independently, and the verification must be recorded.

Article 194. Materials weighed for each batch must be kept together and visibly labeled as such.

Section VI

Manufacturing Operations: Intermediate and Bulk Products

Article 195. Before any process operation is started, measures must be taken to ensure that the work area and the equipment are clean and free from any raw materials, products, product residues, or documents not necessary for the current operation.

Article 196. Intermediate and bulk products must be kept under appropriate conditions.

Article 197. Critical processes must be validated.

Article 198. Any necessary in-process controls and environmental controls must be carried out and recorded.

Article 199. Any significant deviation from the expected yield must be recorded and investigated.

Section VII

Packaging Materials

Article 200. The selection, qualification, approval, and maintenance of suppliers of materials for primary packaging and printed materials must receive similar attention to that given to raw materials.

Article 201. Printed materials must be stored in properly secure conditions in order to prevent unauthorized access.

Sole paragraph. Cut labels and other loose printed materials must be stored and transported in closed and separate containers to avoid mixing.

Article 202. Packaging materials must be separated for use by authorized personnel only, following an approved and documented procedure.

Article 203. Each delivery or batch of primary packaging material or printed material must receive a specific reference number or identification mark.

Article 204. Outdated or obsolete primary packaging material or printed material must be destroyed, and such disposal must be recorded.

Section VIII

Packaging Operations

Article 205. When setting up a program for packaging operations, special attention must be given to minimizing the risk of cross-contamination, mixtures, or replacements.

Sole paragraph. In order to minimize the risk referred to in the caption of this article, different products should not be packed in closely, unless there is physical segregation.

Article 206. Before packaging operations start, measures must be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any previously used products, materials, or documents in case they are not required for the current operation.

Sole paragraph. The line release must be carried out in accordance with to an appropriate checklist.

Article 207. The name and batch number of the product being handled must be displayed at each packaging station or line.

Article 208. All products and packaging materials to be used must be checked upon delivery to the packaging department, regarding quantity, identity, and compliance with the Packaging Instructions.

Article 209. Filling containers must be clean before filling.

Sole paragraph. Any contaminants, such as glass shards and metal particles, must be avoided and removed.

Article 210. Filling and sealing must be followed as quickly as possible by labelling.

Sole paragraph. If this is not the case, appropriate procedures must be applied to ensure that there are no mix-ups or labeling errors.

Article 211. The correct performance of any printing operation (for example, code numbers, expiration dates), to be done either separately or in the course of packaging, must be verified and recorded.

Sole paragraph. Double attention must be given to manual printing, which must be reassessed at regular intervals.

Article 212. Special care must be taken when using cut labels and when overprinting is performed outside the production line.

Sole paragraph. Labels packaged in a roll are more suitable than cut and loose units.

Article 213. Verifications must be made to ensure that any electronic code reader, tag counters, or similar devices are operating correctly.

Article 214. Printed or embossed information on packaging materials must be distinct and resistant to fading or erasure.

Article 215. On-line control of the product during packaging must include, at least, the verification of the following items:

I – general appearance of the packages;

II – if the packages are complete;

III – if the correct packaging products and materials were used;

IV – if the printings applied during the packaging process are correct; and

V – the correct functioning of line monitors.

Article 216. Samples taken from the packaging line cannot be returned.

Article 217. Products that were involved in an unusual event may only be reintroduced into the process after special inspection, investigation, and approval by authorized personnel.

Sole paragraph. A detailed record of this operation must be kept.

Article 218. Any significant or unusual discrepancy observed during the reconciliation of quantity of bulk product and printed packaging materials and the number of units produced must be investigated and satisfactorily accounted for, prior to release.

Article 219. Upon completion of a packaging operation, any unused coded packaging materials must be destroyed, and their destruction must be recorded.

Sole paragraph. If uncoded printed materials are returned to stock, a documented procedure must be followed.

Section IX

Finished Products

Article 220. Finished products must be kept in quarantine until their final release, under the conditions established by the manufacturer.

Article 221. The assessment of finished products and the required documentation before the release of the product for sale is described in Chapter VII of this Resolution.

Article 222. After release, finished products must be stored as usable stock under the conditions established by the manufacturer.

Section X

Rejected, Recovered, and Returned Materials

Article 223. Rejected materials and products must be clearly identified as such and stored separately in restricted areas.

Paragraph 1. The materials and products referred to in the caption of this article must be returned to the suppliers or, where appropriate, reprocessed or destroyed.

Paragraph 2. Any action taken must be approved and recorded by authorized personnel.

Article 224. The reprocessing of rejected products must be an exceptional event.

Paragraph 1. The reprocessing referred to in the caption of this article must be carried out only if the quality of the final product is not affected, if the specifications are complied with, and if it is done in accordance with a defined and authorized procedure, after an assessment of the risks involved.

Paragraph 2. A record of the reprocessing must be kept.

Article 225. The total or partial recovery of previous batches that comply with the quality required for incorporation into a batch of the same product, at a defined stage of manufacture, must be authorized in advance.

Paragraph 1. The recovery referred to in the caption of this article must be carried out in accordance with a defined procedure after assessing the risks involved, including any possible effect on the validity period.

Paragraph 2. The recovery must be recorded.

Article 226. The need for additional testing of any finished product that has been reprocessed, or in which a recovered product has been incorporated, must be considered by the Pharmaceutical Quality Management System.

Article 227. Products returned from the market, and which have left the manufacturer's control, must be destroyed, unless their quality is satisfactory.

Paragraph 1. The products referred to in the caption of this article, the quality of which is satisfactory, may be considered for resale, repackaging, or recovery in a subsequent batch, only after they have been critically assessed by the Pharmaceutical Quality Management System, in accordance with a written procedure.

Paragraph 2. Regarding the verification of the quality referred to in the caption and Paragraph 1 of this article, the nature of the product, any special storage conditions required, its condition and history, and the time elapsed since its issuance must be considered in this assessment.

Paragraph 3. When there is any doubt about the quality of the product, it should not be considered suitable for reuse or recovery, although basic chemical reprocessing to recover the active ingredient may be possible.

Paragraph 4. Any action taken must be properly recorded.

Section XI

Product Shortages Due to Manufacturing Restrictions

Article 228. The manufacturer must notify the marketing authorization holder about any restrictions on manufacturing operations that could result in an abnormal supply restriction.

Sole paragraph. The notification referred to in the caption of this article must be carried out timely in order to facilitate the communication of the supply restriction by the marketing authorization holder to the competent authorities, in accordance with Collegiate Board Resolution – RDC no. 18 of 4 April 2014, or any other that may succeed it.

CHAPTER VII

QUALITY CONTROL

Section I

Introduction

Article 229. Quality Control is responsible for sampling, specifications, and tests, as well as the organization, documentation, and release procedures that ensure required and relevant tests are carried out, that materials are not released for use, nor products released for sale or supply, until their quality has been considered satisfactory.

Article 230. Quality Control is not limited to laboratory operations but must be involved in all decisions that may affect product quality.

Article 231. The independence of Production Quality Control is considered essential for the proper functioning of Quality Control.

Section II

General Provisions

Article 232. Each holder of a manufacturing authorization must have a Quality Control Department.

Article 233. The Quality Control Department must be independent from the other departments.

Article 234. The Quality Control Department must be under the authority of a person with adequate qualifications and experience, with one or several control laboratories at his or her disposal.

Article 235. Adequate resources must be made available to ensure that all Quality Control activities are performed effectively and reliably.

Article 236. The Quality Control Department has the following responsibilities:

I – establish, validate, and implement all quality control procedures;

II – supervise the control of reference and/ or retention samples of materials and products when applicable;

III – ensure the correct labeling of material and product containers;

IV – guarantee the monitoring of product stability; and

V – participate in the investigation of complaints related to product quality.

Sole paragraph. The operations referred to in this article must be carried out in accordance with written procedures and, when necessary, recorded.

Article 237. The evaluation of the finished product must cover all relevant factors, including, but not limited to:

I – production conditions;

II – results of in-process tests;

III – review of manufacturing documentation (including packaging);

IV – compliance with the specification of the finished product in its primary packaging; and

V – evaluation of the product in its final packaging.

Article 238. Quality Control personnel must have access to production areas for sampling and investigation purposes, as appropriate.

Section III

Good Laboratory and Quality Control Practices

Article 239. Laboratory equipment cannot be routinely moved between high-risk areas, in order to avoid accidental cross-contamination.

Article 240. The microbiology laboratory must be organized in a way that minimizes the risk of cross-contamination.

Article 241. Laboratory personnel, facilities, and equipment must be appropriate to the tasks imposed by the nature and scale of manufacturing operations.

Article 242. The use of external laboratories, in accordance with the principles detailed in this Resolution, may be accepted for particular reasons, provided it is stated in the Quality Control records.

Subsection I

Documentation

Article 243. The following documents must be readily available to the Quality Control Department:

I – specifications;

II – procedures describing sampling, tests, records (including test sheets and/ or laboratory record books), and their respective verification;

III – procedures and records for the calibration/ qualification of instruments and maintenance of equipment;

IV – procedure for the investigation of out-of-specification and out-of-trend results;

V – test reports and/ or certificates of analysis;

VI – environmental monitoring data (air, water, and other utilities), when necessary; and

VII – validation records of analysis methods, when applicable.

Article 244. Any Quality Control documentation relating to a batch record must be maintained in accordance with the document retention requirements of this Resolution.

Article 245. Some types of data, such as test results, yields, environmental controls, must be recorded in a way that allows for a trend assessment.

Sole paragraph. Any data outside of trend or specification must be addressed and subjected to investigation.

Article 246. In addition to the information that is part of the batch documentation, other raw data, such as books and/ or laboratory records, must be kept and readily available.

Subsection II

Sampling

Article 247. Sampling must be performed and recorded in accordance with written and approved procedures, including the following:

I – the sampling method;

II – the equipment to be used;

III – the quantity of the sample to be collected;

IV – instructions for any necessary subdivision of the sample;

V – the type and condition of the sample container to be used;

VI – the identification of sampled recipients;

VII – any special precautions to be observed, especially regarding the sampling of sterile or harmful materials;

VIII – the storage conditions; and

IX – instructions for cleaning and storing sampling equipment.

Article 248. The samples must be representative of the batch of materials or products from which they are collected.

Article 249. Other samples may also be collected to monitor the most stressed part of a process, such as the beginning or end of a process.

Article 250. The sampling plan used must be adequately justified and based on a risk management approach.

Article 251. Sample containers must be labeled indicating the content, with the batch number, the sampling date, and the containers from which the samples were collected.

Article 252. Containers must be managed in a way that minimizes the risk of mixing and protects the samples from adverse storage conditions.

Subsection III

Analyses

Article 253. Analytical methods must be validated.

Article 254. A laboratory that is using an analytical method and has not performed the original validation must verify the suitability of the test method during its transfer.

Article 255. All tests described in the record or specification must be performed in accordance with approved methods.

Sole paragraph. The results obtained from the tests must be recorded.

Article 256. The results of the parameters identified as critical quality attributes must be analyzed for trends and verified to ensure they are consistent with each other.

Article 257. Any calculations must be critically analyzed.

Article 258. The tests performed must be recorded, and the records must contain at least the following data:

I – name of the material or product and, when applicable, pharmaceutical form;

II – batch number and, if applicable, manufacturer and/ or supplier;

III – references to relevant specifications and test procedures;

IV – test results, including observations and calculations, and reference to any certificates of analysis;

V – test dates;

VI – initials of the people who performed the test;

VII – initials of the people who verified the tests and calculations, when appropriate;

VIII – clear statement of approval or rejection (or other status decision) and dated signature by the designated responsible person; and

IX – reference to the equipment used.

Article 259. All in-process controls, including those carried out in the production area by the production personnel, must be carried out in accordance with the methods approved by the Quality Control, and the results must be recorded.

Article 260. The quality of laboratory reagents, solutions, glassware, reference standards, and culture media must be specified.

Paragraph 1. The materials referred to in the caption of this article must be prepared and controlled in accordance with written procedures.

Paragraph 2. The verifications and tests carried out on the materials referred to in the caption of this article must be proportional to their use and the stability data available.

Article 261. The reference chemical substances must be suitable for their intended use.

Paragraph 1. The reference chemical substances must be prepared and controlled in accordance with written procedures.

Paragraph 2. The verifications and tests carried out with the reference chemical substances must be proportional to their usage and to the stability data available.

Paragraph 3. The qualification and certification of reference chemical substances must be clearly stated and documented.

Article 262. Whenever there are pharmacopoeial reference chemical substances from an officially recognized source, these should preferably be used as primary reference chemical substances, unless technically justified.

Paragraph 1. The use of work chemical substances is allowed, provided that their traceability to reference chemical substances has been demonstrated and documented.

Paragraph 2. Compendial pharmacopoeial reference chemical substances must be used for the purpose described in the appropriate monograph.

Article 263. Laboratory reagents, solutions, reference chemical substances, and culture media must be identified with the date of preparation and opening as well as the signature of the person who prepared them.

Paragraph 1. The expiration date of reagents and culture media must be indicated on the label, along with the specific storage conditions.

Paragraph 2. For volumetric solutions, the last standardization date and the last correction factor must be indicated.

Article 264. When necessary, the date of receipt of any substance used for testing, such as reagents, solutions, reference and standard chemical substances, must be indicated on the container.

Sole paragraph. Instructions for use and storage must be followed.

Article 265. It may be necessary to carry out an identification test and other tests in reagents before use.

Article 266. The culture medium must be prepared in accordance with the medium manufacturer's requirements, unless technically justified.

Article 267. The performance of all culture media must be verified prior to use.

Article 268. Culture media and microbiological strains used must be decontaminated, following a standard procedure, and disposed of in a manner that avoids cross-contamination and waste retention.

Article 269. The validity of microbiological media in use must be established, documented, and technically justified.

Article 270. Animals used in tests, where appropriate, must be quarantined before use.

Paragraph 1. The animals must be maintained and controlled in order to guarantee their suitability for the intended use.

Paragraph 2. The animals must be identified, and adequate records must be kept, showing the history of their usage.

Section IV

Follow-up Stability Program

Article 271. After commercialization, the stability of the medicinal product must be monitored according to a continuous and adequate program that allows the detection of any stability issues associated with the formulation.

Article 272. The purpose of the follow-up stability program is to monitor the product during its shelf life and determine whether the product remains within the specifications under the storage conditions stated on the label.

Article 273. The follow-up stability program primarily applies to the medicinal product in the package in which it is sold, but the inclusion of bulk products in the program should also be considered.

Article 274. The impact on the stability of the packaged product must be evaluated and studied under long-term stability conditions when the bulk product is stored for a long period before being packaged and/ or shipped from a manufacturing site to a packaging site.

Paragraph 1. The stability of intermediate products that are stored and used for long periods must be evaluated.

Paragraph 2. The stability of the reconstituted product must be evaluated if it is impacted by the bulk product storage conditions.

Article 275. The follow-up stability program must be described in a protocol.

Article 276. The equipment used for the follow-up stability program, stability chambers, among others, must be qualified and maintained in accordance with the requirements of this Resolution.

Article 277. The protocol for a follow-up stability program must be extended until the end of the validity period, and it must include, but not be limited to, the following parameters:

I – number of batch(es) per concentration and different batch sizes, if applicable;

II – relevant physical, chemical, microbiological, and biological testing methods;

III – acceptance criteria;

IV – reference to methods of analysis;

V – description of the packaging closing system(s);

VI – test intervals (points of analysis);

VII – description of storage conditions, and the conditions standardized in the specific regulation in force must be used; and

VIII – other applicable parameters specific to the medicinal product.

Article 278. The set of parameters evaluated in the protocol for the follow-up stability program may be different from the initial long-term stability study, as presented in the marketing authorization dossier, provided that it is duly justified and documented in the protocol.

Article 279. The number of batches and the frequency of testing must provide sufficient data to enable trend analysis.

Article 280. At least one batch per year of products manufactured in all concentrations and in all types of primary packaging must be included in the stability program, unless justified otherwise.

Article 281. The frequency of tests can be altered, considering a risk-benefit relation, for the products where follow-up stability requires animal testing and there are no suitable alternative methods.

Article 282. The principles of grouping and matrixing may be applied to stability studies, if scientifically justified in the protocol.

Article 283. Specific situations may require the inclusion of additional batches in the follow-up stability program, including:

I – in the event of significant alterations or deviations related to the process or packaging; and

II – in the event of reprocessing or recovery operations.

Article 284. The results of follow-up stability studies must be made available to key personnel and particularly to the Technical Responsible Officer.

Article 285. When follow-up stability studies are carried out in a location other than where the bulk or finished product is manufactured, there must be a written agreement between the parties involved.

Article 286. The results of follow-up stability studies must be available at the manufacturing site for review by the competent authority.

Article 287. Significant atypical trends or out-of-specification results must be investigated.

Article 288. Any confirmed result out of specification, or with a significant negative trend, which affects the batches of products released to the market, must be communicated to the competent authorities.

Article 289. The possible impact on the batches on the market must be considered in consultation with the competent authorities.

Article 290. A summary must be written and maintained of all data generated, including any interim conclusions on the follow-up stability program.

Sole paragraph. The summary referred to in the caption of this article must be submitted to regular reviews.

Section V

Technical Transfer of Analytical Methods

Article 291. Before the transfer of an analytical method is initiated, there must be a verification whether it complies with what was approved in the product marketing authorization or relevant technical dossier.

Article 292. The original validation of the analysis method(s) must be reviewed to ensure compliance with the specific regulation.

Article 293. Before starting the process of technical transfer of an analytical method, a failure analysis must be performed and documented to identify any need for further validation.

Article 294. The transfer of analytical methods from one laboratory to another must be described in a detailed protocol.

Article 295. The transfer protocol must include, but not be limited to, the following parameters:

I – identification of the tests to be performed and the relevant test method(s) being transferred;

II – identification of additional training requirements;

III – identification of standards and samples to be tested;

IV – identification of any special conditions of transportation and storage of the items of the test; and

V – the acceptance criteria that must be based on the current methodology validation study and their relationship with the specific regulation in force.

Article 296. Deviations from the protocol must be investigated before closing the process of methodology transfer.

Article 297. The transfer report must document the comparative outcome of the process and it must identify the points that require any need for original revalidation.

CHAPTER VIII

OUTSOURCED ACTIVITIES

Section I

Introduction

Article 298. Any outsourced activity the scope of which is subject to the GMP must be properly defined, agreed, and controlled, in order to avoid misunderstandings that could result in a product or operation of unsatisfactory quality.

Article 299. There must be a written contract between the Contractor and the Contracted company, which clearly sets out the roles and responsibilities of each party.

Article 300. The Contractor's Quality System must clearly describe how the person delegated by the Pharmaceutical Quality Management System exercises his/ her authority regarding the release of each batch of product.

Section II

General Provisions

Article 301. There must be a written contract covering the outsourced activities, products, or operations to which they relate, and any technical agreements signed in relation to them.

Sole paragraph. All arrangements for outsourced activities, including any proposed alterations in technical or other devices must comply with the regulations in force and the product marketing authorization.

Article 302. When the product marketing authorization holder and the product manufacturer are not the same legal entity, appropriate agreements must be signed, in compliance with the provisions of this chapter.

Section III

Contractor

Article 303. The Contractor’s Quality System must include the control and review of any outsourced activities.

Article 304. The Contractor is responsible for ensuring that processes are in place to guarantee the control of outsourced activities.

Sole paragraph. The processes referred to in the caption of this article must incorporate principles of Quality Risk Management and contemplate the following aspects:

I – before outsourcing the activities, the Contractor is responsible for assessing the legality, suitability, and competence of the Contracted company to successfully carry out the outsourced activities;

II – the Contractor is responsible for ensuring through the contract that GMP principles and guidelines, as interpreted in this regulation, are complied with;

III – the Contractor must provide the Contracted company with all information and knowledge necessary to carry out the subcontracted operations correctly in accordance with the regulations in force and with the marketing authorization of the product at issue;

IV – the Contractor must ensure that the Contracted company is notified of any problems associated with the product or work, which may pose a risk to its facilities, equipment, personnel, other materials, or other products; and

V – the Contractor must monitor and review the Contracted company's performance and the identification and implementation of any necessary improvements.

Article 305. The Contractor is responsible for reviewing and assessing the records and the results related to outsourced activities.

Article 306. The Contractor must ensure, on its own account or on the basis of confirmation from the Contracted company's Quality Unit, that all products and materials delivered to it by the Contracted company have been processed in accordance with the GMP and the product marketing authorization.

Section IV

Contracted Company

Article 307. The Contracted company must have the necessary conditions to satisfactorily perform the work requested by the Contractor, through adequate facilities, equipment, knowledge, experience, and competent personnel.

Article 308. The Contracted company must ensure that all products, materials, and knowledge delivered to it are suitable for their intended purpose.

Article 309. The Contracted company must not transfer to third parties any work entrusted to it under the contract, without the prior assessment and approval of the Contractor.

Sole paragraph. Agreements signed between the Contracted company and any third party must ensure that the information and knowledge, including those arising from the third party's suitability assessment, are made available in the same way as between the Contracted company and the Contractor.

Article 310. The Contracted company is prohibited from making unauthorized alterations, outside the terms of the Contract, which may adversely affect the quality of the activities outsourced to the Contractor.

Article 311. The Contracted company must be aware that outsourced activities, including analysis of contracts, may be subject to inspection by the competent authorities.

Section V

Contract

Article 312. A contract must be drawn up between the Contractor and the Contracted company, in which their respective responsibilities and communication processes related to outsourced activities are specified.

Article 313. The technical aspects of the contract must be elaborated by competent people, adequately informed about the related outsourced activities and about the Good Manufacturing Practices.

Article 314. All agreements signed for outsourced activities must comply with the regulations in force, to the marketing authorization of the product at issue, and the terms must be agreed by both parties.

Article 315. The contract must clearly describe which party is responsible for conducting each stage of the outsourced activity, for example knowledge management, technology transfer, supply chain, subcontracting, quality and purchase of materials, testing and release of materials,

as well as carrying out production and quality controls, including in-process controls, sampling, and analysis.

Article 316. All records related to outsourced activities, such as manufacturing, analytical, and distribution records, as well as reference samples, must be maintained or be available to the Contractor.

Article 317. Any records relevant to the assessment of the quality of a product in the event of complaints, suspected deviations, or information for the investigation of suspected counterfeiting must be accessible and specified in the Contractor's specific procedures.

Article 318. The contract must allow the Contractor to audit outsourced activities performed by the Contracted company, or its mutually agreed subcontracted companies.

CHAPTER IX

COMPLAINTS AND PRODUCT RECALL

Section I

Introduction

Article 319. There must be appropriate system and procedures to record, assess, investigate, and review complaints, including possible quality deviations; and, if necessary, to recall medicinal products intended for human use, including experimental medicinal products, effectively and immediately, from the distribution network.

Article 320. The Quality Risk Management principles must be applied to the investigation and assessment of quality deviations, and to the decision-making process for corrective, preventive actions, and other risk reduction actions in relation to the product.

Article 321. When there is evidence of deviation in the quality of a medicinal product, the health authority must be informed, in accordance with the specific legislation, when the deviation may result in product recall or reduction in its offer to the market.

Article 322. In the case of outsourced activities, there must be a contract in which the role and responsibilities of the manufacturer, the marketing authorization holder, and/ or the sponsor are described, as well as the pertinent role and responsibilities of any other third parties in relation to the assessment, decision-making, information dissemination, and implementation of risk reduction actions related to a defective product.

Sole paragraph. The contract referred to in the caption of this article must include the contact information for all responsible people of each party for the management of quality deviations and recall issues.

Section II

Personnel and Organization

Article 323. Adequately trained and experienced personnel must be responsible for managing investigations of complaints and quality defects, as well as for deciding the measures to be taken in order to manage any potential risk posed by such matters, including recalls.

Paragraph 1. The personnel referred to in the caption of this article must be independent from the organization of sales and marketing, unless there is a plausible justification for another procedure.

Paragraph 2. If the Technical Officer Responsible for the certification to release the batch or batches at issue is not part of the team responsible for the actions referred to in the caption of this article, he/ she must be formally informed of any investigations, risk reduction actions, and recall operations, in a timely manner.

Article 324. Trained personnel and sufficient resources must be made available for handling, evaluation, investigation, and review of complaints and quality deviations, with a view to implementing any risk reduction actions.

Sole paragraph. Trained personnel and sufficient resources must be made available for the management of interactions with the health authorities of the countries with which the company has commercial relations.

Article 325. The use of interdisciplinary teams should be considered, including staff properly trained in Quality Management.

Article 326. In situations where the handling of complaints and quality deviations is centrally managed within an organization, the roles and relative responsibilities of the parties involved must be documented.

Sole paragraph. Centralized management should not, however, result in delays in investigation and management of the problem.

Section III

Procedures for Handling and Investigation of Complaints, Including Possible Quality Deviations

Article 327. There must be written procedures outlining the actions to be taken after the receipt of a complaint.

Article 328. All complaints must be documented and evaluated with a view to identifying whether they represent a possible quality deviation or other problem.

Article 329. Particular attention must be given to the receipt of a complaint or suspected quality deviation related to counterfeiting.

Article 330. Complaints that do not indicate a quality deviation, but represent a possible adverse effect, must be documented and communicated to the group or person responsible for the investigation and managements of complaints of such nature.

Article 331. Procedures must be in place to facilitate a request for an investigation of the quality of a batch of a medicinal product in order to support an investigation into the notification of a suspected adverse event.

Article 332. When a quality deviation investigation is initiated, procedures must be implemented to address at least the following items:

I – description of the reported quality deviation;

II – determination of the quality deviation extent;

III – verification or testing of reference and/ or retention samples and, in certain cases, a review of the batch production record, the batch certification record, and the batch distribution records (especially for temperature sensitive products);

IV – need of requesting a sample or return of the defective product from the complainant and, when a sample is provided, an appropriate assessment must be carried out;

V – assessment of the risk(s) presented by the quality deviation, based on its seriousness and extent;

VI – decision-making process to be adopted, in relation to the potential need to take risk reduction actions in the distribution network, such as batch or product recalls or other actions;

VII – assessment of the impact that any recall action may have on the availability of the medicinal product to patients in any affected market, and the need to notify the relevant authorities of such impact;

VIII – internal and external communications that must be carried out in relation to a quality deviation and its investigation;

IX – identification of the potential root cause(s) of the quality deviation; and

X – need for appropriate Corrective and Preventive Actions (CAPAs) to be identified and implemented for the issue, as well as for evaluating the effectiveness of such CAPAs.

Section IV

Investigation and Decision Making

Article 333. The information reported in relation to possible quality deviations must be recorded, including all original details.

Article 334. The validity and extent of all reported quality deviations must be documented and evaluated in accordance with the principles of Quality Risk Management, in order to support decisions regarding the level of investigations and actions taken.

Article 335. If a quality deviation is identified in a batch, consideration must be given to the verification of other batches and, in some cases, other products, in order to determine if they have also been affected.

Sole paragraph. Other batches that may contain deviated batch parts or components must be investigated.

Article 336. Investigations into quality deviations must include the review of records of past quality deviations or any other information relevant to any indication of specific or recurring issues that require attention and possibly other regulatory actions.

Article 337. Decisions made during and after investigations into quality deviations must reflect the level of risk presented by the deviation, as well as the severity of any non-compliance found in relation to the marketing authorization, the product specifications, or the Good Manufacturing Practices.

Paragraph 1. The temporality of the actions referred to in the caption of this article must be appropriate and correlated with the risk level of the deviation to ensure that patient safety is maintained.

Paragraph 2. Actions to reduce risk must be part of the decision-making process, within an appropriate period, even if the information necessary to understand the nature and extent of the deviation is not present at the beginning of the investigation.

Paragraph 3. All decisions and measures taken as a result of a quality deviation must be documented.

Article 338. Quality deviations must be timely communicated by the manufacturer to the marketing authorization holder/ sponsor and all relevant health authorities, in the cases where the quality deviation could result in the recall of the product or in market shortage.

Section V

Root Cause Analysis and Corrective and Preventive Actions

Article 339. Root cause analysis must be applied during an investigation of quality deviations.

Sole paragraph. In cases where the true root cause(s) of the quality deviation cannot be determined, consideration should be given to the possibility of identifying the most likely root cause(s) and addressing it (them).

Article 340. When human error is suspected or identified as the cause of a quality deviation, it must be formally justified to ensure that real causes related to processes, procedures, or systems are not masked and neglected.

Article 341. Appropriate corrective and preventive actions must be developed and adopted in response to quality deviations.

Sole paragraph. The effectiveness of corrective and preventive actions must be monitored and assessed.

Article 342. Records of quality deviations must be regularly reviewed, and trend analyses must be regularly applied to indicate recurrent deviations that require additional attention.

Section VI

Recall of Products and Other Actions to Reduce Risks

Article 343. There must be written procedures that are regularly reviewed and updated, to determine recall activities and other risk mitigation actions.

Article 344. After a product has been distributed to the market, any withdrawal from the distribution network due to quality deviation must be considered and managed as a recall.

Sole paragraph. Recall does not apply to the recovery or return of samples of the product from the distribution network to facilitate an investigation into a quality problem or deviation.

Article 345. There must be the capability to carry out recall operations at any time.

Sole paragraph. In certain cases, it may be necessary to initiate recall operations, in a view to protecting patients, before determining the root causes and understanding the extent of the deviation.

Article 346. Batch/ product distribution records must be readily available to the people responsible for the recall.

Article 347. The distribution records must contain sufficient information about wholesalers and directly supplied clients, even for exported products and medical samples.

Article 348. In the case of medicinal products intended for clinical trials, all trial sites must be identified, and the countries of destination must be indicated.

Paragraph 1. In the case of medicinal products intended for clinical trials for which a health marketing authorization was issued, the medicinal product manufacturer must, in cooperation with the study sponsor, inform the marketing authorization holder of any quality defect that may be related to the authorized medicinal product.

Paragraph 2. The sponsor must implement a procedure for the rapid disclosure of the products subject to blinded randomized trials, when this is necessary for an effective recall.

Paragraph 3. The sponsor must ensure that the procedure discloses the identity of the product being tested in the blinded randomized trial to the extent that this is strictly necessary for the recall.

Article 349. An analysis must be carried out on the extent of the recall action in the product distribution network, which considers the risks to the patient, after consulting with the health authority.

Article 350. The health authority must be informed in the cases where a proposed recall action is not carried out due to the expiration of the medicinal product validity period.

Article 351. All interested health authorities must be informed in advance in the cases where there is an intention to recall.

Paragraph 1. In very serious situations, that is, those with the potential to cause serious impacts to the patient's health, it may be necessary to take rapid risk reduction measures before notifying the competent authorities.

Paragraph 2. Whenever possible, the measures must be agreed with the competent authorities, before their execution.

Article 352. Consideration must be given to whether the proposed recall action may affect different markets in different ways, and, if so, appropriate market-specific risk mitigation actions must be developed and discussed with the competent health authorities.

Article 353. The risk of shortage of a medicinal product that does not have an authorized alternative, considering its therapeutic use, must be considered before deciding on a risk reduction measure such as a recall.

Sole paragraph. Any decision not to take a risk reduction action that would otherwise be necessary must be agreed in advance with the competent authorities.

Article 354. The recalled products must be identified and stored separately in a secure location while they wait for a decision on their destination.

Sole paragraph. A formal disposal of all recalled batches must be issued and documented.

Article 355. The justification for any decision to reprocess the recalled products must be documented and discussed with the health authority.

Article 356. The extension of the remaining shelf life for any reprocessed batch that could be put back on the market must be considered with the health authority.

Article 357. The progress of the recall process must be recorded until completion.

Article 358. A final report on the recall must be issued, including a reconciliation between the delivered and recovered quantities of the products/ batches at issue.

Article 359. The effectiveness of the recall system must be periodically assessed for the confirmation that it remains robust and suitable for use.

Paragraph 1. The assessments referred to in the caption of this article must be carried out during working and non-working hours.

Paragraph 2. Simulated recall actions must have a documented and justified assessment about when they should be used.

Article 360. In addition to recalls, other risk mitigation actions may be considered to manage the risks presented by quality deviations.

Paragraph 1. The actions referred to in the caption of this article may include the issuance of preventive communications to health professionals regarding the use of a potentially deviating batch.

Paragraph 2. The actions must be considered on an individual basis, and must be discussed with the competent health authorities at issue.

CHAPTER X

SELF-INSPECTION

Article 361. Self-inspections must be carried out to monitor implementation and compliance with the principles of Good Manufacturing Practices, and propose the necessary corrective measures.

Article 362. Issues related to personnel, facilities, equipment, documentation, production, quality control, distribution of medicinal products, procedures for managing complaints and recalls, as well as self-inspection, must be examined on a regular basis, following a pre-established program in order to verify their compliance with the principles of Quality Assurance.

Article 363. Self-inspections must be conducted independently and in detail by competent person(s) designated by the company.

Sole paragraph. Independent audits, carried out by external experts, may be used.

Article 364. All self-inspections must be recorded.

Article 365. The reports must contain all observations made during the inspections and, where applicable, proposals with corrective measures.

Article 366. Statements about actions taken subsequently must also be recorded.

CHAPTER XI

FINAL PROVISIONS

Article 367. Item VII of Article 8 of this Resolution came into force on 7 April 2020.

Article 368. Article 10 of this Resolution came into force on 7 January 2020.

Article 369. The normative requirements of articles 74, 75, 76, and 77, contained in this Resolution, do not apply to medicinal gas companies.

Article 370. For the companies to adapt and meet the regulatory requirements contained in Article 172 of this Resolution, the following deadlines are hereby established:

I – by 7 April 2020, companies must have already completed the (re)structuring/ integration activities for their Pharmaceutical Quality and Risk Management Systems; qualified and trained their employees (from different departments if they are involved in productive operation activities, including mainly cross-contamination risk management/ control); identified and hired qualified services/ professionals (trained toxicologist professional; training; with expertise and practical experience) for the determination of the Allowed Daily Exposure values of the products, in order to subsidize the reassessments of the maximum allowed residual limits carried between products, with regard to validations of cleaning procedures for equipment surfaces in contact with products;

II – by 7 October 2020, when any (commercial and experimental) products are introduced in production lines, companies must have already fully complied with the new regulatory requirement;

III – by 7 October 2021, companies must have fully complied with the new regulatory requirement for 30% of all (commercial and experimental) products in the portfolio;

IV – by 7 October 2022, companies must fully comply with the new regulatory requirement for 60% of all (commercial and experimental) products in the portfolio; and

V – by 7 October 2023, companies must fully comply with the new regulatory requirement for 100% of all (commercial and experimental) products in the portfolio.

Article 371. The requirements of Article 179 of this Resolution became effective for legacy products on 7 October 2020.

Sole paragraph. Legacy products are those already granted marketing authorization.

Article 372. Article 215 of this Resolution becomes effective on 7 October 2024.

Paragraph 1. The actions described below must have proof of execution, in accordance with the deadlines established as follows:

I – by 7 October 2020, the Elaboration of User Requirements and the prospection of manufacturers must have already been carried out;

II – by 7 April 2021, the selection of the manufacturer and the Design Qualification must have already been carried out;

III – by 7 October 2021, the purchase must have already been confirmed;

IV – by 7 October 2023, the installation of the equipment must be carried out; and

V – by 7 October 2024, the other stages of equipment qualification necessary for the compliance with Article 215 and its start-up in the routine must be carried out.

Paragraph 2. The qualification stages not referred to in the transitoriness established in the caption and in Paragraph 1 and its items of this Article shall not be interpreted as not necessary.

Article 373. The general rules provided for in this Resolution are complemented by the specific guidelines published by the Normative Instructions linked to this Resolution.

Article 374. This Resolution authorizes the Health Inspection General-Office (GGFIS, in Portuguese) to develop the document “Dynamic Questions & Answers for the Guidelines of Good Manufacturing Practices for Medicinal Products”, to be published on Anvisa's website, with the technical interpretation and guidance, to be used during inspections, referring to the provisions contained in this Resolution and in the Normative Instructions linked to it.

Sole paragraph. The first version of and subsequent alterations in the document specified in the caption of this article must be presented and approved at a Public Meeting of Anvisa Collegiate Board of Directors.

Article 375. The classification of establishments that manufacture medicinal products and pharmaceutical inputs regarding compliance with Good Practices is established by the respective Standard Operating Procedures of the Brazilian National Health Surveillance System harmonized at a tripartite level and published on Anvisa's website.

Article 376. Certification of Good Manufacturing Practices for Medicinal Products and Pharmaceutical Inputs, in accordance with the requirements of this Resolution, the Normative Instructions linked hereto, and Collegiate Board Resolution – RDC no. 69 of 8 December 2014, or any other that may succeed it, has the concession criteria established by the respective Standard Operating Procedures of the Brazilian National Health Surveillance System harmonized at a tripartite level and published on Anvisa's website.

Sole paragraph. The production lines that must be included in the certificate are established by Standard Operating Procedures of the Health Inspection General-Office and published on Anvisa's website.

Article 377. Regarding active pharmaceutical ingredients called atypical, the lack of proof of compliance with the Good Manufacturing Practices must be justified observing the principles of Quality Risk Management, in order to enable the use of the material in the manufacture of medicinal products.

Paragraph 1. The premise of the possibility of using the ingredients referred to in the caption of this article lies in their unavailability on the market as a pharmaceutical input.

Paragraph 2. As a justification for the non-compliance with the relevant good practices, there must be proof that the input referred to is found in practice only as, for example, an input of food or cosmetics industry.

Paragraph 3. The risk assessment of the use of this atypical pharmaceutical ingredient in the manufacture of medicinal products must consider the extent to which the applicable Good

Manufacturing Practices were complied with by the manufacturer and, consequently, the acceptability of the risks associated with the points not complied with.

Paragraph 4. The absence of information, the difficulty of access to the manufacturer of the atypical active pharmaceutical ingredient, or commercial issues do not justify the use of the inputs referred to without the appropriate Risk Management.

Article 378. Failure to comply with the provisions of this Resolution shall subject the violator to the penalties provided for in Law no. 6,437 of 20 August 1977, and other complementary legislation, without prejudice to the applicable administrative, civil, and criminal sanctions.

Article 379. The following are hereby revoked:

I – Collegiate Board Resolution – RDC no. 301 of 21 August 2019;

II – Collegiate Board Resolution – RDC no. 388 of 26 May 2020; and

III – Collegiate Board Resolution – RDC no. 580 of 26 November 2021.

Article 380. This Resolution enters into force on 2 May 2022.

ANTONIO BARRA TORRES