GPIE
EIPG

Code of Practice

for QUALIFIED PERSONS

EUROPEAN INDUSTRIAL PHARMACISTS GROUP

E.I.P.G.

European Industrial Pharmacists Group

E.I.P.G. is a European association representing the national, professional organizations of pharmacists employed in the pharmaceutical or allied industries of the Member States of the European Union, the European Economic Area, or European countries having a mutual recognition agreement with the European Union on compliance control of regulated medicines.

Its foundation dates back to 1966 and, over the years, it has progressed in its activities in line with the evolution of the European Union.

Today EIPG represents about 10 000 pharmacists working in the European Industry The group is recognized within the EU as one which collectively represents a European view on behalf of all industrial pharmacists in EU. This is an important principle when consulting with, or offering views and opinions to European Union organizations and regulatory bodies.

The group maintains contact with the European Commission and several meetings have been held between EIPG and representatives from the Commission.EIPG has also met representatives from EMA and is one of the interested parties with whom the agency may communicate on matters of mutual interest.

Website: eipg.eu

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Presentation

This Code of Practice has been conceived with the aim of offering an updated view of the legal and technical requirements pertaining to the position of the Qualified Person (QP) in Europe.

The added value of this document is represented by the comments and recommendations which have been added to each requirement, taking into account the practical experience of many European industrial pharmacists in their role of QPs.

Apart from this paper version, the document is also available in an electronic form which is accessible to all EIPG members through the EIPG website.

In fact, it is the scope of this document to provide a living Code of Practice by ensuring a constant updating as a consequence of the introduction of new European requirements pertaining to the QP and considering the possible integration of new comments based on the contributions of EIPG members.

Authors and Contributions

This document has been prepared by a select group of EIPG members who were charged with issuing a first draft based on a plan which had been discussed and approved by the EIPG Bureau.

The initial draft was made available to all EIPG members through the delegates which are present in each European country association of industrial pharmacists.

The observations and suggestions received were duly considered for the preparation of the final version which was submitted to the EIPG board of directors for the approval.

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Contents

1. Introduction

The concept of the Qualified Person (QP), first established in 1975, is a unique regulatory requirement, which applies only within the European Union (EU). The only comparable situation exists within Member States of the European Economic Area (EEA) with whom the EU has reciprocal agreements.

Each holder of an authorization to manufacture or import human, veterinary medicinal products, or Advance Therapeutic Medicinal Product (ATMPs) or Investigational Medicinal Products (IMPs) within Member States of the EU, must name a person or persons who are eligible to act in the capacity of a Qualified Person.

The following requirements are in force:

- The requirement for QP covers both Human and Veterinary Medicinal Products, IMPs and ATMPs, including those intended for exportation outside the EU
- Particular conditions for formal qualifications and practical experience for eligibility to act as a QP are specified in the relevant EU Council Directives. Ensuring compliance with these conditions is the responsibility of the Competent Authorities of the EU Member States and eligibility requirements are described in local regulations
- The primary legal responsibility of the QP is to certify batches of Investigational Medicinal Products prior to use in a Clinical Trial (Human Medicinal Products only) or to certify licensed Medicinal Products prior to release for sale and placing on the market (Human and Veterinary Medicinal Products or ATMPs). However, in some EU states the legal responsibility is that of the supervisory pharmacist as well as the delegated QP who may have certified release of a particular batch.
- The peculiar duties of the QP involved in IMP management, as well as the specific regulatory basis, are addressed in Addendum 1

2. Regulatory Basis

The Qualified Person must ensure that all legislative obligations are fully satisfied before any product is certified and released for sale. Therefore, a Qualified Person must have a comprehensive knowledge of all current European and national legislation relating to the manufacture, storage and supply of investigational and licensed medicinal products, relative to the member state in which these products are to be supplied.

The key regulatory documents and the specific articles concerning the Qualified Person are reported as follows:

A. Directives and Regulations

a. **Directive 2001/83/EC** – Community Code Relating to Medicinal Products for Human Use – Title IV – Manufacture and Importation – **Articles 40-53**

b. **Directive 2001/82/EC** – Community Code Relating to Veterinary Medicinal Products – Title IV – Manufacture and Imports – **Articles 44-57**

c. **Directive 2001/20/EC** – Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use – **Article 13**

d. **Directive 2005/28/EC** – Principles and Detailed Guidelines for Good Clinical Practice as regards Investigational Medicines Products for Human Use, as well as the Requirements for Authorisation of the Manufacturing or Importation of Such Products – Chapter 3 – Manufacturing or Import Authorisation – **Articles 9-15**

e. **Directive 2003/94/EC** – Principles and Guidelines of Good Manufacturing Practice for Medicinal Products for Human Use – **Art 7**

f. **Directive 91/412/EEC** – Principles and Guidelines of Good Manufacturing Practice for Veterinary Medicinal Products – **Art 7**

g. **Commission Delegated Regulation (EU) 2017/1569** – Principles and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials) – **Art 6**

h. **Directive (EU) 2017/1572** – supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials) – **Art 7**

i. **Regulation (EC) 1394/2007** – on advanced therapy medicinal products (ATMPs), amending Directive 2001/83/EC and Regulation (EC) 668/2019 implementing Regulation (EC) 1394/2007 with regard to the evaluation and certification of quality and non-clinical data relating to ATMPs developed by SMEs.

j. **Directive 2011/62/EU (FMD)**, amending Directive 2001/83/EC

k. **Delegated Regulation 161/2016**, defining the requirements for safety features application as requested by the **Directive 2011/62/EU**

B. Guidelines

a. EudraLex Volume 4 – Good Manufacturing Practices (GMP) Guidelines:

- **Part I** - Chapters1-9
- **Part III** - Annex 1 – 19 (in particular Annex 16)
- **Part IV** – GMP Requirements for Advanced Therapy Medicinal Products

b. EMAGuidance

- EMA Guidance 196292/2014 "Qualified Person's declaration concerning GMP compliance of the active substance manufacture "The QP declaraation template"

c. "QP Code of Practice": the joint document issued by the Royal Pharmaceutical Society, Royal Society of Biology and Royal Society of Chemistry, November 2018

3. Purpose of the Code

- The purpose of this Code of Practice is to provide operational guidance for carrying out the functions of the QP considering his/her responsibilities and in the light of the professional Code of Conduct, as required by **Article 52 of Directive 2001/83/EC and by Article 56 of Directive 2001/82/EC**.
- The duties and responsibilities of the QP are stated in **Article 51 of Directive 2001/83/ EC** and in **Article 55 of Directive 2001/82/ EC**.
- This Code of Practice is aimed at clarifying and supporting QPs in developing their activities in full compliance with the legal requirements with the interest of their referring Marketing Authorization Holders and with the consideration of patients.
- This Code could be used as a reference for considering any disciplinary procedure against a QP in case of failure to fulfil his/her obligations, as required by **Article 52 of Directive 2001/82/EC** and by **Article 56 of Directive 2001/82/EC**.

4. Application of the Code

This Code of Practice is equally applicable to QPs who have achieved their status under the transitional arrangements or under the permanent provisions of the relevant Directive, and who are named on Marketing Authorisations as the "Technical Director" or "Responsible Pharmacist "(Pharmacien Responsible), hereafter referred to as the QP.

This Code applies equally to QPs involved in human, veterinary medicines, ATMPs or IMPs.

QPs have a professional duty to decline to act as QPs in certifying product categories for which they do not possess the relevant experience and knowledge.

The terminology used in this Code of Practice corresponds to that used in the relevant, up to date, EU Directives and corresponding guidelines on GMPs.

5. Code of Conduct (Ethics)

Qualified Persons must maintain exemplary standards of integrity, competence, objectivity, honesty, courage, fairness and respect in all aspects of their work – and have a personal and professional responsibility to ensure that every batch of product certified for release ensures the standards of Quality, Safety and Efficacy.

Qualified Persons must be competent to perform the services for which they have been hired and expected to perform. As quality professionals, they must commit themselves to continual learning, while being able to acknowledge areas that are outside of their expertise.

Qualified Persons must act in an objective manner. As quality professionals, they must base their decisions on factual information. They must not be unduly influenced by competing or conflicting interests.

Qualified Persons must have integrity. As quality professionals, they must be principled and consistent in applying their views. They must live up to their commitments, and be trustworthy and scrupulous at all times.

Qualified Persons must be honest in all dealings with their employers and the regulatory competent authority with whom they interact. As quality professionals, they must ensure that information and communications, whether oral or written, are accurate and complete. Qualified Persons acknowledge that personal and institutional credibility is crucial to their success.

Qualified Persons must have the courage to make difficult decisions and present all relevant information to their organisations in order to promote wise decisions. As quality professionals, they must be able to withstand challenges to their views, while at the same time be accountable for their mistakes.

Qualified Persons must be fair in their dealings with all parties. As quality professionals, they must apply legal and regulatory standards equitably. They must be fair in considering the interests of all parties in decision processes.

Qualified Persons must be respectful of others, whether it is their peers, subordinates or external parties with whom they interact. As quality professionals, they must treat all individuals with dignity and courtesy.

Qualified Persons must maintain transparency, honesty and sound probity in all financial

and commercial matters both within their own companies and when dealing with, or acting on behalf of, clients.

6. General Principles

Qualified Persons have a primary duty to ensure that all products certified and released for use comply with the standards registered with the local Competent Authority in compliance with the laws and regulations of both the European Union and the Member State under which they operate are consistent with the principles of the Pharmaceutical Quality and with the best practice in the manufacture of medicines

7. Professional Development

Maintaining competence throughout a career during which new and challenging professional responsibilities will be encountered is a fundamental ethical obligation for all those working in the pharmaceutical industry.

This is particularly important for the Qualified Persons involved with the batch release of medicinal products

There is a general requirement on pharmaceutical companies who hold Marketing Authorizations (MAs) '....to take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods..' (Article 23 of Directive 2001/83/EC).

This can only be achieved by a personal commitment to Continuing Professional Development (CPD).

It is the responsibility of each QP for systematic maintenance, development and broadening of knowledge and skills, to ensure continuing competence as a professional, throughout their careers.

The process should be visible to ensure credibility to the public.

A structured programme of CPD must be actively managed to be effective and should include:

- Self-appraisal
- Personal plan
- Participation
- Action (implementation)
- Evaluation

It must be an ongoing, cyclical process of continuous quality improvement by which the Qualified Person seeks to maintain and enhance their competence in both current duties and anticipated future service developments.

Professional development is becoming more and more important taking int account the introduction of advanced technological solutions in manufacturing (e.g. continuous manufacture) and control of medicinal products. It is essential that a QP keep constantly

informed and develop an appropriate plan for updating his/her knowledge in consideration of the new requirements to be considered.

8. Areas of Authority and Responsibility

8.1 Pharmaceutical Quality System

The presence of an appropriate Pharmaceutical Quality System is the basic requirement for the manufacture and control of medicinal products. **Chapter 1 of EU GMP Part I** describes the specific requirements for establishing, implementing and maintaining an effective quality system.

However, quality requirements are also reported in other chapters of EU GMP Part I, where specific reference is made to personnel, premises, equipment and quality control activities.

Out of the **9 chapters of EU GMP** covering all the manufacturing activities, the following excerpts of **Chapters 1**, **2**, and **4** are reported, highlighting the specific requirements involving QP duties and responsibilities in managing an appropriate quality system.

Chapter 1 - Principles

*All parts of the Pharmaceutical Quality System should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorisation and for the **Qualified Person(s)**.*

➔Comment

The system in place should be regularly challenged through self-inspections and on the basis of the results of audits (by customers) and inspections (by authorities).

Furthermore, the quality system can be periodically assessed by applying Key Performance Indicators, which are to be developed in accordance with the Senior Management directions and in agreement with the specificity of the company manufacturing processes.

Chapter 1 – 1.4 (v) and (xv)

A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:

*(v) Managerial **responsibilities** are clearly specified*

➔Comment:

The main duties, responsibilities and skills of each key function (manager) must be defined, appropriately documented (Job descriptions) and formally shared and accepted by the QP and the Senior Management.

In the organization chart, the QP position is to be clearly identified, proving his/her independent responsibilities line and the formal connection with the other key functions.

(xv) Medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;

➔Comment

Written and detailed manufacturing and control instructions must be in place, in accordance with the Manufacturing Authorization documents (Common Technical Documents).

In particular, a specific SOP describing the batch certification process within the organization should be present.

Prompt revision must be applied to these procedures, in case of variation or introduction of updated references.

Chapter 1 – 1.5 and 1.6

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

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

➔Comment

A Quality Committee, including the senior management, should be established for a periodic Quality Review. QP should be a member of this committee.

Appropriate Balance Score Cards, KPIs and quality results must be periodically discussed.

Senior Management should be, in particular, involved in decision making regarding critical and major issues.

Planning and a written summary of each committee, and the related decision are taken, should be in place. Periodical quality review and continuous improvement principles should be applied.

Independence in the decision making and corresponding authority of a QP must be put in writing in order to ensure the absence of influence of the business driver in the critical quality issue.

Chapter 2 –Principles

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

➔Comment

The application of these principles is satisfied by the presence of appropriate job descriptions covering all key positions and a suitable training plan. As far as the QP, his/her educational and professional profile is to be documented, proving its suitability to the company needs in releasing medicinal products.

Chapter 2 –General

2.2 The manufacturer must have an organisation chart in which the relationships between the heads of Production, Quality Control and where applicable Head of Quality Assurance or Quality Unit referred to in point 2.5 and the position of the Qualified Person(s) are clearly shown in the managerial hierarchy.

➔Comment

Quality functions, represented by QA and QC or by a QU, should be reported in the organization chart, proving their independence from Production. The independent responsibilities of the QP should be evident in the same organization chart.

2.3 People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of that personnel concerned with the application of Good Manufacturing Practice.

➔Comment

Duties and Responsibilities of the QP's Deputy should be defined in writing, as an addendum of the primary Job Description of the involved function. Experience and skills assessment by the QP in order to verify the adequacy should formally be included.

2.4 ***Senior management*** *has the ultimate responsibility to ensure an effective quality management system is in place to achieve the quality objectives, and, that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality and should ensure continuing suitability and effectiveness of the quality management system and GMP compliance through participation in management review.*

➔Comment

The quality policy should be implemented and published in order to formally state the overall intention and direction of the company related to quality and should ensure continuing suitability and effectiveness of the quality management system and GMP compliance through participation in management review.

2.5 ***Senior Management*** *should appoint Key Management Personnel including the head of Production, the Head of Quality Control, and if at least one of these persons is not responsible for the duties described in Article 51 of Directive 2001/83/EC, an adequate number, but at least one, Qualified Person(s)designated for the purpose. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent of each other.*
In large organisations, it may be necessary to delegate some of the functions listed in 2.7 (Head of Production Department), 2.8 (Head of Quality Control) and 2.9 (Head of Production, Head of Quality Control, Head of Quality Assurance, Head of Quality Unit).

Additionally depending on the size and organisational structure of the company, a separate Head of Quality Assurance or Head of the Quality Unit may be appointed.
Where such a function exists, usually some of the responsibilities described in 2.7, 2.8 and 2.9 are shared with the Head of Quality Control and Head of Production and senior management should, therefore, take care that roles, responsibilities, and authorities are defined.

➔Comment

These requirements highlight that different organizations are accepted, as a function of the company size, provided that key responsibilities and authorities are assigned by senior management to QP.

2.6 The duties of the ***Qualified Person(s)*** *are described in Article 51 of Directive 2001/83/EC, and can be summarised as follows:*

a) for medicinal products manufactured within the European Union, a ***Qualified Person*** *must ensure that each batch has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorisation;*

(b) in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the European Union a ***Qualified Person*** *must ensure that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation. The Qualified Person must certify in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 51.*

The persons responsible for these duties must meet the qualification requirements laid down in Article 49 of the same Directive, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities.

The responsibilities of a Qualified Person may be delegated, but only to other ***Qualified Person(s)****.*

Guidance on the role of the ***Qualified Person*** *is elaborated in Annex 16.*

➔Comment

Batch Review is one of the most critical aspects that should be properly managed in order to support and facilitate the role of the QP in the certification and release of a batch. In case of a batch manufactured and/or packaged by third parties or other sites of the same company, a proper Quality/Technical Agreement, including a matrix of responsibilities, should be in place in order to ensure that all the critical quality/technical aspects are covered. An exhaustive check-list should be adopted to verify that all the performed activities are properly carried out and any deviation assessed, addressed and removed.

Chapter 2 –Training

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

2.14 The pharmaceutical quality system and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

➔ Comment

A continuous training program should be established and implemented for all the personnel, considering the impact of each function on the quality system. A specific training plan for new employees should be designed in order to ensure the exploitation of each rule impacting on the quality. For managing and documenting employee training, an appropriate system is required to be adopted. As an example, a matrix can be prepared for each employee to ensure that all the instructions and knowledge of his/her specific function are satisfied and continuously updated, based on each new issuing of rules and related quality documents. A final assessment of the understanding of each topic treated in a training session should be documented. A minimum target of correct responses to a test verification should be preliminarily established to define the acceptability of the test.
A matrix, prepared for each employee to ensure that all the instructions and knowledge of his/her specific function are satisfied and continuously updated, based on each new issuing of rules and related documents, should be the best option but other instruments could be used for the scope.

(4.11) Specific requirements apply to batch documentation which must be kept for one year after the expiry of the batch to which it relates or at least five years after certification of the batch by the ***Qualified Person****, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion of formal discontinuation of the last clinical trial in which the batch was used. Other requirements for retention of documentation may be described in legislation in relation to specific types of product (e.g. Advanced Therapy Medicinal Products) and specify that longer retention periods be applied to certain documents.*

(4.12) For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing The authorisation should be retained whilst the authorization remains in force.
...
The quality management system should describe all documents required to ensure product quality and patient safety.

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

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

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

➔ Comment

A Quality Manual should be in place to cover all the aspects related to document management and data integrity in order to satisfy the expectations regarding criteria regulating:

- **documents' distribution and traceability**
- **documents' modification, review and update (i.e. index of changes)**
- **documents 'expiration**
- **data storage**

The data must be secured against damage by both physical and electronic means. For computerized systems, the following considerations are made:

- **If the data is transferred to another data format or system, the validation must include checks that the data is not altered in value and/or in meaning during the migration process**
- **If relevant changes are made to computer systems, the ability to retrieve the data must be guaranteed: the accessibility, readability and integrity of these data should be checked**
- **Backups of all relevant data should be made regularly: the integrity and accuracy of data backups and the ability to restore data must be checked during validation and monitored periodically**

8.2 Batch Certification and Release

The batch certification and release are the key actions which complete the whole process of manufacture and control of medicinal products, allowing the shipment and distribution on the market. In particular, batch certification is, for sure, the most delicate and complex duty for a QP, who has to consider and evaluate the overall compliance of operations which have been carried out within the appropriate Pharmaceutical Quality System.

The main reference document is Annex 16 to EU GMP, which describes the detailed requirements for a QP, in terms of duties and responsibilities.

Excerpts from **Annex 16**, where QP duties and responsibilities are highlighted, are reported together with some comments.

Annex 16 – General Principles

*The **QP** is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State where certification takes place, in accordance with the requirements of the marketing authorisation (MA) and with Good Manufacturing Practice (GMP).*

The process of batch release comprises of:

i. The checking of the manufacture and testing of the batch in accordance with defined release procedures.

*ii. The certification of the finished product batch performed by a **QP** signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch.*

*iii. The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the **QP**. If this transfer is performed at a site other than that where certification takes place, then the arrangement should be documented in a written agreement between the sites.*

➔ Comment

These requirements highlight the process steps, which are to be followed for each batch release and specify the duties of the QP. These requirements are to be transferred in appropriate formal procedures, which are being written based on the company size and organization. In fact, taking into account the peculiarity of the products to be released and the extension of documentation and data to be checked, QP will have to rely on experienced staff for completing all verifications as required for batch certification.

Annex 16 – The Process of Certification

(1.1) Each batch of the finished product must be certified by a QP within the EU before being released for sale or supply in the EU or for export. Certification can only be performed by a QP of the manufacturer and/or importer which are described in the MA.

➔ Comment

Certification is to be considered the most important duty a QP and it is to be emphasized that certification should be based on his/her full awareness of the correct performance of all manufacturing and testing operations.
This implies that QP has to have not only a good understanding of GMPs but also a deep knowledge of the manufacturing technologies which are applied, keeping constantly informed and updated on any change or improvement, in conformity with the MA specifications.

*(1.2) Any **QP** involved in the certification, or confirmation of a batch must have detailed knowledge of the steps for which they are taking responsibility. The QP should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP.*

➔ Comment

It is evident that, in case of the introduction of new products or new technology, QP has to be adequately trained, documenting his/her extended knowledge in the appropriate records.

*(1.3) There may be several sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification. Regardless of how many sites are involved, the **QP** performing certification of the finished product must ensure that all necessary steps have been completed under accepted pharmaceutical quality systems to assure compliance of the batch with GMP, the MA and any other legal obligations in the Member State where certification is taking place.*

➔ Comment

The increasing complexity of the supply chain at the global level makes the described situation more and more frequent. The requirements highlight that the QP, who releases the finished product has to take full responsibility of ascertaining that all certification steps made before the last one have been appropriately carried out in agreement with the MA specifications. It is essential to set up a written agreement between all QP involved in the manufacturing chain, where all MA specifications are reported, including a complete and reliable procedure which is to be followed for ensuring timely communications between all actors.

*(1.4) For manufacturing steps performed at sites in the EU, each manufacturing site must have at least one **QP**.*

➔ Comment

It is recognized that, according to the company size, there could be more than one QP. This possibility implies clear evidence in the organization chart and the presence of written procedure defining how responsibilities are assigned to the QPs and how they are managed according to a different situation (time, competencies, interactions, decision making).

*(1.4.1) Where the site only undertakes partial manufacturing operations in relation to a batch, then a **QP** at that site must at least confirm that the operations undertaken by the site have been performed in accordance with GMP and the terms of the written agreement detailing the operations for which the site is responsible. If the **QP** is responsible for providing confirmation of compliance for those operations with the relevant MA, then the **QP** should have access to the necessary details of the MA.*

➔ Comment

This requirement makes reference to the situation where, for technical or economic reasons, partial operations (e.g. film coating, secondary packaging, labelling, others) are outsourced. In fact, besides the third party qualification and signing a quality agreement, it is highlighted the importance that, where compliance is relevant with the MA (risk assessment of the partial

manufacturing operation), the third-party QP has to have access to all details of the MA, provided that a confidentiality agreement has been signed.

*(1.4.2) The **QP** who performs certification of the finished product batch may assume full responsibility for all stages of manufacture of the batch or this responsibility may be shared with other **QPs** who have provided confirmation for specified steps in the manufacture and control of a batch. These could be other **QPs** who are operating under the same manufacturing authorisation (MIA) holder or **QPs** operating under different MIA holders.*

➔ Comment

This requirement confirms that the QP, performing the finished product certification and release, has to take full responsibility, taking charge of verifying that all previous certifications of operations involved in the manufacturing chain have been carried out in compliance with the MIA in place, considering all MIA holders involved.

*(1.4.3) Any sharing of responsibilities amongst **QPs** in relation to compliance of a batch must be defined in a document formally agreed by all parties. This document should detail responsibility for assessment of the impact any deviation(s) has/have on compliance of the batch with GMP and the MA*

➔ Comment

This requirement specifies that the formal agreement among QPs is to be complete in terms of full compliance with the MA details and full compliance with the applied quality system, including assignment of responsibilities for non-conformance assessment during all operations.

(1.5) For medicinal products manufactured outside the EU, physical importation and certification are the final stages of manufacturing which precede the transfer to the saleable stock of the batch.

(1.5.1) The process of certification as described in Section 1 of this Annex, applies to all medicinal products intended to be released for the EU markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.

*(1.5.2) In accordance with the principles described in Section 1.4 of this Annex, the **QP** certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, **other QPs** in relation to any manufacturing or importation operations taking place at other sites in the EU and other manufacturing authorisation holders defined in the relevant MA.*

➔ Comment

Once again, taking into account the complexity of the supply chain, the QP who releases the product has always to consider the other QPs who have been concerned with the manufacture or importation process of the same product, ensuring that each QP has taken full responsibility of his/her part of the process.

*(1.5.3) Conditions of storage and transport for the batch and the sample, if sent separately, should be taken into account by the **QP** before certification of a batch.*

➔ Comment

The verification of storage conditions is part of the actions taken for confirming the compliance to quality requirements, before batch certification. This verification should be part of a procedure in place.

*(1.5.4) The **QP** certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. Unless an MRA or similar agreement is in place between the EU and the exporting country, the **QP** is also responsible for ensuring that the finished medicinal product batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products is in accordance with the requirements of the MA.*

➔ Comment

In order to meet these requirements, there should be a procedure describing how to collect and document all information and data which are to be made available for the QP certification.

*(1.5.7) Different imported finished product batches may originate from the same bulk product batch. The **QPs** certifying the different finished product batches may base their decision on the quality control testing of the first imported finished batch provided that justification has been documented based on Quality Risk Management principles.*

➔ Comment

According to this specific requirement, a quality risk assessment of the whole supply chain should include any situation where a "first imported product" is controlled and used.

*(1.6) The **QP** must personally ensure that the following operational responsibilities are fulfilled prior to certification of a batch for release to market or for export:*

i. Certification is permitted under the terms of the MIA.
ii. Any additional duties and requirements of national legislation are complied with.
iii. Certification is recorded in a register or equivalent document.

➔ Comment

This requirement highlights some critical formal verifications which are to be performed prior to batch certification. The importance of these verifications is stressed making reference to "operational responsibilities", which can be assigned to qualified personnel, and to the specific task of the QP to ensuring compliance. In order to manage this duty, there should be an adequate procedure describing in details the actions to be made in due time before any batch certification.

*(1.7) In addition, the **QP** has responsibility for ensuring the following points (from 1.7.1 to 1.7.21) are secured. These tasks may be delegated to appropriately trained personnel or third parties. It is recognised that the **QP** will need to rely on the pharmaceutical quality system and the **QP** should have an on-going assurance that this reliance is well-founded.*

(1.7.1) All activities ... conducted according to GMP

*(1.7.2) The entire supply chain ... up to the stage of certification is documented and available for the **QP**.*

*(1.7.3) All audits of sites ... have been carried out and that the audit reports are available to the **QP** performing the certification.*

(1.7.4) All sites ... are compliant with the terms of the MA for the intended territory

(1.7.5) All activities ... are consistent with those described in the MA.

(1.7.6) ... Supplier quality management systems are in place

(1.7.7) ... the active substances have been manufactured in accordance with GMP and, where required, distributed according to GDP

(1.7.8) The importation of active substances ... should comply with the requirements

(1.7.9) ... the excipients have been manufactured in accordance with the ascertained GMP

(1.7.10) ... TSE status of all materials ... is compliant with the terms of the MA.

(1.7.11) All records are complete and endorsed by the appropriate personnel...

(1.7.12) All manufacturing and testing processes remain in the validated state. Personnel are trained and qualified as appropriate

(1.7.13) Finished product quality control (QC) test data complies with the Finished Product Specification described in the MA

(1.7.14) Any regulatory post-marketing commitments ... have been addressed. On-going stability data continues to support certification.

(1.7.15) The impact of any change ... has been evaluated and any additional checks and tests are complete.

(1.7.16) All investigations ... have been completed ...

(1.7.17) Any on-going complaints, investigations or recalls do not negate the conditions for certification of the batch in question.

(1.7.18) The required technical agreements are in place.

(1.7.19) The self-inspection programme is active and current.

(1.7.20) The appropriate arrangements for distribution and shipment are in place.

(1.7.21) In the case of medicinal products for human use intended to be placed on the market in the Union, the safety features referred to in Article 54(o) of Directive 2001/83/EC, as amended, have been affixed to the packaging, where appropriate.

➔ Comment

The above requirement reports the complete list of verifications tasks that any QP has to make, in agreement with his/her responsibilities. It is evident that all these tasks cannot be personally completed by the QP.
As stated in the beginning, the QP may delegate these tasks to appropriately trained personnel or even to third parties.
The key point stays in the adequate organization which is to be developed and managed for dealing with all these tasks.

(1.9)In the case of parallel importation and parallel distribution any repackaging operation carried out on a batch which has already been released must be approved by the competent authority of the intended market.

*(1.9.1) Prior to certification of a repacked batch, the **QP** should confirm compliance with national requirements for parallel importation and EU rules for parallel distribution.*

*(1.9.2) The **QP** of the MIA holder, who is named responsible for the certification of the batch in the MA of the repackaged finished product, certifies that the repackaging has been performed in accordance with the relevant authorisation pertaining to the repackaged product and GMP.*

➔ Comment

Repackaging of products coming from parallel importation and parallel distribution is a delicate operation, requiring the strict application of the procedure which has been approved by the Competent Authorities.
In this case, the QP is responsible to ascertain the full quality compliance of the repackaging operations, verifying that they are carried out in accordance with the relevant authorization. For completing this duty, he/she has to set up a suitable quality procedure to ensure that the repackaging instructions meet the officially approved specifications.

*(1.10) Recording of **QP** certification.*

(1.10.1)The certification of a medicinal product is recorded by the QP in a register or equivalent document provided for that purpose. The record should show that each production batch satisfies the provisions of Article 51 of Directive2001/83/EC, as amended, or Article 55 of Directive 2001/82/EC. The record must be kept up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years.

➔ Comment

The batch certification is the formal act the QP has to draw up before the formal batch release (moving the batch to the saleable stock).
The certification requires to be documented appropriately, establishing a suitable register, which will be complying with the internal procedure about documentation management (including data integrity), taking into account that this act is to be produced at any time on request of Health Authorities.

Annex 16 – Relying on GMP Assessment by Third Parties

*In some cases, the **QP** will rely on the correct functioning of the pharmaceutical quality system of sites involved in the manufacture of the product and this may be derived from audits conducted by third parties.*

*(2.2. iv) The **QP** should ensure that a written final assessment and approval of third-party audit reports have been made. The **QP** should have access to all documentation which facilitates a review of the audit outcome and continued reliance on the outsourced activity.*

➔ Comment

The reliance on third parties has become a common practice in order to meet all GMP requirements, which have progressively increased due to the increased complexity of the supply chain and the increased number of actors involved in the manufacture and control of products.
On this respect, the requirements are very clear: even though the use of third parties is allowed on a contract basis, the responsibility remains on the QP.
As a consequence, it is essential to rely on qualified third parties, by selecting the most appropriate for the action being concerned and by keeping their activities under suitable control.

Annex 16- Handling of Unexpected Deviations

*Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, a **QP** may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical control methods from details contained within the MA and/or GMP has occurred. The deviation should be thoroughly investigated and the root cause corrected. This may require the submission of a variation to the MA for the continued manufacture of the product.*

➔ Comment

This requirement highlights the discretion degree the QP can employ when an unexpected deviation occurs with respect to the details of the MA and the GMP compliance.
Even though this would allow the QP to manage unexpected deviations, performing investigations and proposing possible variations to the details of the MA, it is to be observed that only minor events in the manufacture and control processes will be considered, being all registered specifications of API, excipients, packaging materials and finished product to be always in compliance with the MA details. Nevertheless, this is a sound recognition of the key position of the QP in managing all quality issues and it should simplify the application of the procedure about variations.

Annex 16 - The Release of a Batch

*(4.1) Batches of medicinal products should only be released for sale or supply to the market after certification by a **QP** as described above. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant Competent Authority.*

(4.2) Safeguards to ensure that uncertified batches are not transferred to saleable stock should be in place and maybe physical in nature, e.g. the use of segregation and labelling or electronic in nature, e.g. the use of validated computerised systems.
When uncertified batches are moved from one authorised site to another, the safeguards to prevent premature release should remain.

*(4.3) The steps necessary to notify **QP** certification to the site where the transfer to saleable stock is to take place should be defined within a technical agreement. Such notification by a **QP** to the site should be formal and unambiguous and should be subject to the requirements of Chapter 4 of EudraLex, Volume 4, Part I.*

➔ Comment

As already explained, certification is the formal act before the release of a batch, moving it to the saleable stock.
An uncertified batch corresponds to a batch under quarantine and means that all required quality evaluations of its manufacture and its control have not been completed. This is the reason for keeping uncertified batches under strict control avoiding any mix-up with those already certified, which are transferred to saleable stock.
Next to the requirements about physical or electronic segregation of uncertified batches, the QP is requested to adopt appropriate procedures for notifying batch certification to the site where the transfer to a saleable stock takes place.
In particular, taking into account the complexity of the distribution chain, it is requested to define a technical agreement between different actors (the QP and the person in charge of moving the products to saleable stock) to make notification of batch certification unambiguous.

8.3 **Non Conformity Management**

One of the duties of a QP is the identification, assessment and management of any event or result of non-conformity to the established specifications or requirements.

Non-conformities include not only deviations (results out of specifications in manufacture processing and control), quality defects (in quality control testing), complaints (after product shipment and distribution, requiring product recall), but also quality non-compliant results which come out from self-auditing or from customers auditing.

Excerpts of EU GMP **Chapter 8**, where quality non-conformity is discussed, are reported, together with some comments focusing on the duties and responsibilities of the QP.

EU GMP – Chapter 8 – Principles

Quality Risk Management *principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls corrective and preventative actions and other risk-reducing actions.*

All concerned competent ***authorities should be informed*** *in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the* ***recall*** *of the product or an abnormal* ***restriction in the supply***.

➔ Comment

Though all investigations and assessments are part of the tasks assigned to Quality Assurance, this GMP requirement highlights the need for considering the critical level of the non-conformity issue. When this is so high and recall or restriction in distribution are to be evaluated, it is evident that QP will be directly involved for taking the appropriate decision, including information of the competent authorities.

In situations where the product on the market is found to be non-compliant with the marketing authorisation, there is no requirement to notify concerned competent authorities provided the degree of non-compliance satisfies the Annex 16 restrictions regarding the handling of unplanned deviations.

➔ Comment

The unplanned deviations are under the discretion degree of the QP. For this reason, if the situation of non-compliant with the MA satisfies the Annex 16 principles, no notification to authorities is required.

EU GMP – Chapter 8 – Personnel and Organization

Appropriately trained and experienced personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls.
These persons should be independent of the sales and marketing organisation unless otherwise justified.
If these persons do not include the Qualified Person involved in the certification for release of the concerned batch or batches, the latter should be made formally aware of any investigations, any risk-reducing actions and any recall operations, in a timely manner.

➔ Comment

According to the company size and organization, QP can be an active member of the quality compliance team, managing and taking responsibility for complaints and quality defect investigations.
If this is not the case, the QP is to be promptly and formally made aware of the results of these investigations, is responsible for the final decision which will be taken (recall, risk-reducing actions, CAPA plan).

(8.15) Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned ***Competent Authorities*** *in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.*

(8.16) An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.

(8.22) ***Recall operations*** *should be capable of being initiated promptly and at any time. In certain cases recall operations may need to be initiated to protect public or animal health prior to establishing the root cause(s) and the full extent of the quality defect.*

(8.25) Consideration should be given following consultation with the concerned ***Competent Authorities****, as to how far into the distribution network a recall action should extend, taking into account the potential risk to public or animal health and any impact that the proposed recall action may have. The* ***Competent Authorities*** *should also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired (such as with short shelf-life products.)*

(8.26) All concerned ***Competent Authorities*** *should be informed in advance in cases where products are intended to be recalled. For very serious issues (i.e. those with the potential to seriously impact upon patient or animal health), rapid risk-reducing actions (such as a product recall) may have to be taken in advance of notifying the* ***Competent Authorities****.*
Wherever possible, attempts should be made to agree on these in advance of their execution with the concerned ***Competent Authorities****.*
Taking account of its therapeutic use the risk of a shortage of a medicinal product which has no authorised alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action which would otherwise be required should be agreed with the competent authority in advance.

➔ Comment

All the above requirements highlight how quality defects are to be considered and, when required, to be reported to MA Holder and Authorities to be informed. The situation requiring a recall from the market is reported, specifying the critical factors to be considered.
Even the QP is not mentioned, it is evident that he/she would be directly involved in evaluating any situation, in taking the appropriate decision, in informing the MA Holder and in communicating with the Competent Authorities.

(8.31) In addition to recalls, there are other potential risk-reducing actions that may be considered in order to manage the risks presented by quality defects. Such actions may include the issuance of ***cautionary communications to healthcare professionals*** *in relation to their use of a batch that is potentially defective. These should be considered on a case-by-case basis and discussed with the concerned competent authorities.*

➔ Comment

In agreement with the MA Holder, the QP will be involved in any cautionary communication to a healthcare professional, taking into account his/her responsibility of quality compliance and MA conformity.

8.4 Relationship with Suppliers

The quality of starting materials and packaging materials have a direct impact either on the feasibility of the manufacturing process and on the quality of the finished medicinal product.

The qualification of suppliers is a key element for implementing a reliable pharmaceutical quality system.

EU GMP Chapter 5 reports the main requirements for the qualification of suppliers of starting materials (active substance and excipients) and packaging materials (including printed materials).

In the case of active substances, QP responsibilities include the assessment of the compliance of the supplier to EU GMP part II, through a physical audit and the ascertainment and documentation of the supply chain. The second requirement is based on the EMA guidance **EMA/196292/2014**.

Excerpts of the above reference documents are reported together with some comments focusing on the QP responsibilities.

EU GMP Chapter 5 – Starting Materials

(5.27) The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier/material approval should be maintained. Staff involved in these activities should have current knowledge of the suppliers, the supply chain and the associated risks involved. Wherepossible, starting materials should be purchased directly from the manufacturer of the starting material.

➔ Comment

All the above actions are essential tasks to be conducted by competent personnel within the framework of an adequate pharmaceutical quality system. The QP has to express his/her leadership in supporting the personnel involved at all levels and sites within the organization.

(5.28) The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement or specification.

➔ Comment

This is a general requirement defining the details which are to be included in the formal quality agreement or specification. The QP will be involved in the function of the critical issues which could be present in the required documentation, with particular reference to the compliance to the MA details.

(5.29) For the approval and maintenance of suppliers of active substances and excipients, the following is required:

Active substances

Supply chain traceability *should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.*

The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the EEA based manufacturer or importer of the medicinal product.

Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. ***The holder of the manufacturing authorisation*** *shall verify such compliance either by himself or through an entity acting on his behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk.*

Audits *should be of appropriate duration and scope to ensure that a full and clear*

assessment of GMP is made; consideration should be given to potential cross-contamination from other materials on site. The report should fully reflect what was done and seen on the audit with any deficiencies clearly identified. Any required corrective and preventive actions should be implemented.

***Further audits** should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain.*

Excipients

Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment in accordance with the European Commission 'Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use'.

➔ Comment

These requirements highlight the fundamental needs which are to be satisfied in considering the selection and qualification of the key suppliers of API and excipients.

According to the pharmaceutical quality system, procedures defining the objectives to be achieved, the modalities to be followed and the assigned responsibilities are to be present.

The QP will be particularly concerned with the verification, also on behalf of the MA Holder, that manufacturers and distributors of the APIs comply with the GMPs and GDPs.

The QP will have to be involved in the evaluation of the results of the audits and the need of further audits, taking into account the critical level of the supplier, as determined in the quality risk assessment phase.

On the whole, the QP has to keep a constant focus on the compliance of the APIs and excipients suppliers, for their reliability in terms of supply chain traceability, GMP/GDP conformity and meeting all specifications.

(5.36. ii)The medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the marketing authorisation dossier.

➔ Comment

Audits of suppliers are an essential requirement for ascertaining quality compliance by the medicinal product manufacturer. The QP will have to be involved in the definition of an auditing plan and in the evaluation of the results of the audits, taking responsibility of the quality compliance verification of suppliers and the conformity to the MA details.

5.71) The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in an abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations

➔ Comment

The QP will have to be informed about any abnormal restriction in the supply of APIs or excipients, taking appropriate actions for any technical verification before communicating the situation to the MA Holder.

EMA Guidance 196292 / 2014- QP Declaration

*Marketing authorisations require a **QP declaration** to confirm that the manufacture of the active substance complies with GMP, that this is based on an audit and that the audit outcome confirms compliance with GMP.*

Unless covered by an agreement as stated in the next bullet point, a QP declaration is required from each registered EEA manufacturer and Importer Authorisation Holder (MIAH) that uses the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinary medicinal product.

➔ Comment

This guidance was issued for giving detailed explanations on how to ascertain the GMP compliance of API suppliers, providing formal instructions on the details to be reported for documenting the actions taken.

The QP is the main actor in this context and he/she has to count on experienced and qualified personnel for meeting all requirements. In fact, for preparing the QP declaration, it will be necessary to report:

- **the name and address of each manufacturing site, beginning from the first use of the designated starting material**
- **the manufacturing operation/activity of each site (including intermediate sites)**
- **the site address, in detail to ensure that the site is accurate**

As far as the required on-site audit, the following considerations are to be made:

- **the QP has to be aware of the qualification of the auditor when an audit is given to a third party body (based on a contract)**
- **the QP will be responsible for the audit plan and the audit frequency**
- **the QP will be responsible for assessing any exceptional circumstance when an on-site audit is not practical**

The required formal declaration includes the following statements, which are to be signed by the QP:

a) QP responsibility

The signatory confirms that he or she is the authorised QP with specific responsibility for GMP compliance of the active substance manufacture and that audit reports and all other documentation relating to the QP declaration will be made available for inspection by competent authorities if requested.

b) GMP compliance

The signatory confirms that the manufacture of the active substance complies with GMP, that this is based on an audit and that the audit outcome confirms compliance with GMP.

c) Audit

The signatory confirms, in the case of a third-party audit(s), that each contract acceptor has been

evaluated and technical agreements are in place. The signatory also confirms, in all cases, that the audits were conducted by suitably qualified and trained staff.

d) Responsibilities in the case of multiple MIAH(s):

The signatory confirms that the declaration is made on behalf of all the involved QPs named on the relevant MIAH(s), that a documented procedure defining GMP responsibilities is in place and that technical agreement exists between the named companies concerning the management of GMP responsibilities.

8.5 Outsourcing Activities

Any outsourced GMP regulated activity is required to be managed according to the principles of the Quality Management System.
These activities are to be appropriately defined, agreed and controlled in order to avoid misunderstandings, which could result in a product or operation of unsatisfactory quality.

The QP responsibilities are therefore extended to the outsourced GMP activities. **EU GMP Chapter 7** reports the fundamental requirements for managing the relationship with the third party, while **Annex 16 at point 1.5** specifies the conditions for ensuring full responsibility in product batch release when manufacture is performed outside the EU.

Excerpts of the above reference documents are reported together with some comments focusing on the QP responsibilities.

EU GMP – Chapter 7 – Outsourced Activities

Principle

*There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality Management System of the Contract Giver must clearly state the way that the **Qualified Person** certifying each batch of product for release exercises his full responsibility.*

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

➔ Comment

In discussing and defining the outsourced activities, the QP should ascertain that the third party (contractor) will be fully compliant with the GMP general requirements and, in particular, will be able to satisfy all requirements reported in MA of the product to be outsourced

7.4 The pharmaceutical quality system of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles

➔ Comment

There should be an appropriate procedure for managing any outsourced GMP regulated activity.
In order to comply with this requirement, the procedure in place should include the application of the principles of quality risk management in assessing and controlling the operations performed by the contractor.

7.5 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the Contract that the principles and guidelines of GMP as interpreted in this Guide are followed.

➔ Comment

In selecting, identifying and choosing the third party, it is required to consider the following aspects:

- **its manufacturing authorization and any other legal requirements, as necessary for performing the contract activities;**
- **its competencies, in terms of the presence of appropriate material and human resources, as required for performing the contract activities;**
- **its compliance with the GMP.**

7.6 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly

in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

➔ Comment

Once a trustful third party has been chosen, open and clear communication is essential for transferring all information about MA requirements and any other technical issues, which are to be considered for implementing all outsourced operations correctly.
Communication should include the assessment of third party understanding of all critical requirements, by organizing meeting, audits and by keeping the communication constantly open with the third party.

7.7 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.

➔ Comment

Taking into account the critical level of the outsourced activity (to be defined according to a risk assessment), it is necessary to define the conditions for keeping the third party under control, by identifying quality performance indicators of its activity.
The relationship with the third party should be based on collaboration, for the reciprocal benefit, including any improvement of the outsourced activities.

7.8 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He should also ensure, either by himself or based on the confirmation of the Contract Acceptor's Qualified Person, that all products and materials delivered to him by the Contract Acceptor have been processed in accordance with GMP and the marketing authorisation.

➔ Comment

The QP responsibilities include checking of all documents which have been generated by the third party in performing the outsourced activities, as this is required for the complete certification of the batch, before batch release.
A procedure should be developed for determining how this documentation is transferred and which assessment is requested to the third party for proving its compliance with the agreed MA requirements.

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

➔ Comment

The contract should contain all essential requirements and should define responsibilities clearly. Although competent persons should be involved in preparing the contract, the final responsibility in signing stays in the QP, being this contract a fundamental document related to quality and GMP.

7.15 The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).

Comment

➔ The content of the Contract may vary according to the type and the extension of the outsourced activity.
However, it is essential that the Contract contains all elements with the appropriate relevance for managing the outsourced activities, with the complete definition of who does what.

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

➔ Comment

The contract should include a definition of the documents which are required for monitoring the outsourced activities and have been agreed for supporting the final batch certification.
It should be also taken into account of any critical or unexpected issue of non-compliance, which is to be dealt with according to shared procedures, including emergency cases, like the suspicion of falsified products.

7.17 The Contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or his mutually agreed subcontractors

➔ Comment

The Contract should be based on a good relationship between the parties.
An audit of the third party's facilities should be part of the agreement, as it is to be considered an element of the GMP assessment.

Annex 16 - The Process of Certification

1.5 For medicinal products manufactured outside the EU, physical importation and certification is the final stages of manufacturing which precede the transfer to the saleable stock of the batch.

1.5.1 The process of certification as described in Section 1 of this Annex, applies to all medicinal products intended to be released for the EU markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.

1.5.2 In accordance with the principles described in Section 1.4 of this Annex, the QP certifying the finished medicinal product batch may take account of the confirmation by and share defined responsibilities with, other QPs in relation to any manufacturing or importation operations taking place at other sites in the EU and other manufacturing authorisation holders defined in the relevant MA.

1.5.3 Conditions of storage and transport for the batch and the sample, if sent separately, should be taken into account by the QP before certification of a batch.

1.5.4 The QP certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. Unless an MRA or similar agreement is in place between the EU and the exporting country, the QP is also responsible for ensuring that the finished medicinal product batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products is in accordance with the requirements of the MA.

1.5.5 Sampling of the imported product should be fully representative of the batch. Samples may either be taken after arrival in the EU or be taken at the manufacturing site in the third country in accordance with a technically justified approach which is documented within the company's quality system. Responsibilities in relation to the sampling should be defined in a written agreement between the sites. Any samples taken outside the EU should be shipped under equivalent transport conditions as the batch that they represent.

1.5.6 Where sampling is performed at a third country manufacturing site, the the technical justification should include a formal Quality Risk Management the process to identify and manage any risks associated with this approach. This should be fully documented and include at least the following elements:

I. Audit of the manufacturing activity including any sampling activity at the third country site and evaluation of subsequent transportation steps of both the batch and samples to ensure that the samples are representative of the imported batch.

ii. A comprehensive scientific study, including data to support any conclusions that samples taken in the third country are the representative of the batch after importation. This study should at least include:

- *Description of the sampling process in the third country.*
- *Description of the transported conditions of the sample and the imported batch. Any differences should be justified.*
- *Comparative analysis of samples taken in the third country and samples were taken after importation.*
- *Consideration of the time interval between sampling and importation of the batch and generation of data to support appropriate defined limits.*

iii. Provision for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in a third country.

iv. A review of any unexpected result or confirmed out of specification result. These may have implications for reliance on sampling performed at the third country manufacturing site and should be notified to the Supervisory Authority for the site where certification is performed. Such an occurrence should be regarded as a potential quality defect and investigated in line with the guidance in Chapter 8 of EudraLex, Volume 4, Part I.

1.5.7 Different imported finished product batches may originate from the same bulk product batch. The QPs certifying the different finished product batches may base their decision on the quality control testing of the first imported finished batch provided that justification has been documented based on Quality Risk Management principles. This should take into account the provisions of paragraph 1.5.6 in relation to reliance on any samples taken in third countries. Evidence should be available to ensure that the integrity and identity of the imported finished product batch have been established through documented verification of at least the following:

i. Relevant requirements for storage of the bulk product prior to packaging have been satisfied;

ii. The finished product batch has been stored and transported under the required conditions;

iii. The consignment has remained secure and there is no evidence of tampering during storage or transportation;

iv. Correct identification of the product has been established;

v. The sample(s) tested are representative of all finished product batches derived from the bulk batch.

8.6 **Quality Oversight**

It is generally recognized that the QP must have and keep a general oversight on all GMP relevant operations and activities ongoing in the company. This is of utmost importance especially for batch disposition; it is well known that the quality of each batch in terms of safety and efficacy and of regulatory compliance, is not only based on the batch-specific data but also to the efficacy and suitability of the quality system. Only by having the overall picture of the status of all GMP aspects, directly and indirectly impacting on the quality of the batch, the QP will be in the position to make a sound and justified decision about the batch certification and release to the market.

This requirement is well represented by the Annex 16 to EU GMP. While point 1.6 clearly defines activities to be performed personally by the QP, the subsequent point 1.7 indicates the activities that can be delegated, provided he/she has the on-going assurance that this reliance is well-founded.

The QP Code of Practice

In the interpretation of the authors of this document, an activity is delegated when the QP is not part of the process, i.e he/she does not plan, perform, review results or approve any significant step in the activity.

According to **Annex 16**, activities that can be delegated include verification of:

- GMP compliance of all manufacturing and testing activities (batch record review);
- documentation of the complete supply chain, from starting and packaging materials to the finished product, including steps that are outsourced;
- availability of timely performed audits of sites involved in the manufacture and the testing of the medicinal products and in the manufacture of the active substance;
- regulatory compliance of all the sites of manufacture, analysis and certification, and of manufacturing and testing activities;
- management of suppliers in order to ensure only materials of the required quality has been supplied;
- compliance to GMP and GDP of respectively manufacture and distribution of active ingredients;
- compliance with applicable regulations (e.g. in EU) of importation of active ingredients
- compliance to GMP of excipients ;
- compliance with applicable regulations for TSE prevention;
- completeness of all records, including in-process controls and checks;
- validation status of all manufacturing and test processes;
- qualification and training of personnel;
- correspondence of release test results to quality specifications as in the Marketing Authorization;
- commitment with Regulatory Authorities;
- results of ongoing stability studies;
- completion of changes or management of ongoing changes;
- completion of investigations (including OOS and OOT results) on batch deviations;
- impact of any investigation, complaint or recall;
- availability of the necessary technical and quality agreements;
- availability and performance of the self-inspection program ;
- availability of arrangements for distribution and shipment ;
- implementation of anti-counterfeiting and safety measures (e.g. in EU);

➔ Comment

The QP should establish an oversight on all these activities if delegated. Oversight can be established in different ways :

- **planned occasional personal participation in the activity;**
- **regular participation in quality major or critical issues management process (e.g. in case of recalls, significant regulatory actions or major /critical observations left by Authorities during an inspection);**
- **regular participation in quality review meetings, where the activity status or results are reported;**
- **review and approval of reports including quality trending (e.g. Product QualityReviews, Ongoing Process Verification Reports, Microbiology Trend Reports, Annual Quality Reports)**

There should be in place a regular and period review of the efficacy of the delegations, with changes in the organization in case of evidence of non-compliance.

8.7 Relationship with Authorities

The QP should be considered the appointed representative of the Health Authority in the pharmaceutical manufacturing plant or company. He/she should establish effective and transparent contact with the supervising Authority and collaborate in the common task of assuring timely delivery of medicines to patients with the required quality, safety and efficacy.

The collaboration channel should be established first in a preventive mode, making all the necessary actions to assure that only drug products with the required quality and in compliance with the approved dossier reach the patients.

Preventive actions could be :

- provide all the necessary documents and information to prepare the CMC Part of the registration dossier /CTD (e.g. the QP declaration concerning GMP compliance of the active substance manufacture) and to support variations;
- collaborate in answering all deficiency letters and requests received from Authorities during the registration of a new product or variation to a registered one;
- provide all the necessary documents and information to support variations in the manufacturing authorizations and facilitate review and approval of competent Authorities ;
- facilitate inspections by Authorities and support the necessary corrective actions and improvements to products, processes and the quality system

Equally important is to establish a quick and efficient channel of communication in case of quality issues or defects which affect or potentially affect batches or products already distributed on the market or in clinical trials.
This obligation is several times described in EU GMPs.

For instance, in the case of complaints:

*... All concerned competent authorities should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the recall of the product or an abnormal restriction in the supply (**chapter 8, Principle**)*

Again in the same chapter :

*Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product (**8.15**);*

*Consideration should be given following consultation with the concerned Competent Authorities, as to how far into the distribution network a recall action should extend, taking into account the potential risk to public or animal health and any impact that the proposed recall action may have. The Competent Authorities should also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired (such as with short shelf-life products) (**8.25**);*

*All concerned Competent Authorities should be informed in advance in cases where products are intended to be recalled. For very serious issues (i.e. those with the potential to seriously impact upon patient or animal health), rapid risk-reducing actions (such as a product recall) may have to be taken in advance of notifying the Competent Authorities. Wherever possible, attempts should be made to agree on these in advance of their execution with the concerned Competent Authorities (**8.26**)*

Also potential or actual drug shortages are to be considered quality issues to be reported to Authorities. In this case, **chapter 5** of the EU GMP (Production) is very clear:

The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in an abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations (5.71)

8.8 Relationship with the Responsible Person

The Responsible Person is the key person in managing the Quality System of distribution activities, as regulated by the GDPs (see Addendum).

Even though QP has no direct responsibilities in the distribution activities, he/she has to establish and maintain a strict relationship with the Responsible Persons who are present in the distribution of the products which he/she has released.

The main interactions of the Qualified Person (QP) with the Responsible Person (RP) can be summarized as follows.

Depository Warehouse

Depository warehouse is normally the first step taken by a MAH to start the distribution of medicinal products. Depository warehouse can be used as additional storage of products after their release for sale, before shipping them to the wholesalers for their distribution to final customers (community pharmacists, hospitals).
Each depository warehouse has to have a Responsible Person taking responsibilities of GPD compliance.

The QP should be involved in the quality assessment of the depository warehouse, where the released products will be stored. QP should apply appropriate criteria for this quality assessment, taking into account not only his/her knowledge of GMP requirements but also the GDP requirements as requested for the specific storage of the products.
The interaction with the Responsible Person should be focused on transferring all information about the requested storage conditions, based on the stability profile of the products involved.
The QP should, in particular, ascertain that a proper quality system is in place for managing the following key elements:

- SOP for downloading of products from the transportation trailer (goods integrity verification, handling and data registration) and for product allocation in the warehouse (goods identification and recording)
- SOP for controlling, monitoring and recording of the warehouse temperature
- SOP for picking operations and shipment conditions, when a request of distribution is issued

The above critical elements and other more specific requirements should be discussed with the Responsible Person and should be part of a Technical and Quality Agreement, defining the respective responsibilities in communicating data and information according to agreed quality criteria.

Distribution of Products

After depository warehousing, when products are in distribution, other possible interactions of the QP with the Responsible Person is to be considered in the following events:

Transportation Issue
In case of an issue during transportation (temperature excursion above the limits), the Responsible Person, after considering all elements in his/her hands, should communicate with the QP (or a delegated person) in order to discuss any technical detail which could be useful for clarifying the issue and for taking the appropriate decision.

Products Return
In case of return of products from customers (wholesalers, pharmacists, hospitals) due to different reasons (distribution mistake, faulty product, wrong product, others), the Responsible Person has to apply a suitable SOP for handling the returned goods, including identification, verification and storage in a segregated area.
The QP should be informed about this return and a discussion should take place in order to evaluate whether the product can be distributed again or is to be destroyed if the RP has not all necessary information in his/her hands.

Falsified Products
When there is the suspicious that a product is falsified, the Responsible Person has to segregate the product and to immediately communicate with the QP of the MAH for discussing how to proceed in order to definitely ascertain whether the falsification is present.

ADDENDUM **1**

QP RESPONSIBILITIES IN INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs) QUALITY MANAGEMENT

1. **Introduction**

Investigational Medicinal Products (IMPs) are basically different from commercial products: in the first case, the manufacturing process is frequently modified to better support the clinical trials throughout the phases 1, 2 and 3, while the latter one is characterized by a well-defined and validated process.
Specific guidelines and directives have been issued by the European Authority to define specific requirements for these products in order to assure patient safety and scientific validity of the clinical studies.
From a practical point of view, the QPs are accountable to ensure these goals are achieved certifying the IMP batches. In principle, there are no differences from the QPs in charge of marketed products.
Therefore, the aim of this addendum addresses the peculiar activities of the QPs for IMPs in addition to the themes already enlightened in this document.

2. **Regulatory Basis**

The European Parliament approved in 2014 Regulation no. 536 on clinical trials on medicinal products for humans that are currently not in force.
At present, the conduct of a clinical trial and the quality requirements of the IMPs are defined in the EU Directive 2001/20 and related documents.
The implementation of the new Regulation will start 6 months after the publication of the notice referred to in Article 82(3) (536/2014) on the Official Journal of the European Union after the functionality of the EU portal and the EU database have been validated.
From the date, the Regulation entries in force, a transitional period of 3 years both
sets of documents will apply accordingly and should be referred to respectively to the legislation under which the Clinical trial is conducted.
To give a full comprehension of the present and future areas of authority and responsibility of the QPs both sets of documents are reported, but only the current one is commented.
It has to be highlighted that the introduction of EudraLex Vol. 10 provides the following suggestion:

> *Although it is not mandatory, stakeholders are encouraged to take already into consideration a number of aspects that are outlined in the new or updated documents published in the page dedicated to the Clinical Trial Regulation and apply them to those clinical trials authorised under the Directive, to the extent possible and incompatibility with the legal framework of the Directive.*

A. Set of documents applicable to clinical trials authorised under Directive 2001/20/EC

A.1 Directives and Regulations

- **Directive 2001/20/EC** - *Good clinical practice in the conduct of clinical trials on medicinal products for human use* – **Article 13**
- **Directive 2005/28/EC** - *PrinciplesandDetailedGuidelinesforGoodClinical Practice as regards Investigational Medicines Products for Human Use, as well as the Requirements for Authorisation of the Manufacturing or Importation of Such Products – Chapter 3 – Manufacturing or Import Authorisation* – **Articles 9 – 15**
- **Directive 2003/94/EU** - *Principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use* – **Article 7**

A.2 Guidelines

EudraLex Volume 4 – Good Manufacturing Practices (GMP) Guidelines

- **PartI–Chapters1–9**
- **Annexes 13 and 16** (related to manufacturing human medicinal products)

A.3 EMA Guidance

- **The Qualified Person (QP) declaration on** equivalence to EU GMP for Investigational Medicinal Products manufactured in third countries
- **Guidance** on Investigational Medicinal Products (IMPs) and 'Non-Investigational Medicinal Products' (NIMPs) (rev. 1, march 2011)

B. Set of documents applicable to clinical trials that will be authorised under Regulation EU No 536/2014, once it becomes applicable

B.1 Directives and Regulations

- **Regulation (Eu) No 536/2014** - Clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- **Commission Delegated Regulation (Eu) 2017/1569** - Principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspection

B.2 Guidelines

- **Detailed Commission guidelines No C(2017) 8179** on good manufacturing practice for Investigational Medicinal Products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/201
- **Guideline on** the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice (DRAFT)

B.3 EMA Guidance

- **Content of the Batch Certificate for Investigational Medicinal Products** Referred to in Article 62(1) of Regulation (EU) No 536/2014 and Article 4 of Delegated Regulation 1569 /2017
- The **qualified person's (QP) declaration** on equivalence to EU GMP for Investigational Medicinal Products manufactured in third countries

3. Areas of Authority and Responsibility

These comments supplement those already reported in the first part of this document. They address the peculiar tasks and duties a QP should fulfil when dealing with Investigational Medicinal Products

NOTE: The EU Directive and the Annex 13 defines the tasks and duties of the Qualified Person entrusted by the Sponsor in the Clinical Trial Application. Therefore, this QP has been approved by the Competent Authority to conduct this task. Then, it has to highlight that there are two chains of responsibility:

- From a quality perspective: the QP to QP agreement linking every QP working within the supply chain of the IMPs
- From a regulatory perspective: the QP-Sponsor agreement linking their own responsibilities versus the Competent Authority.

4. Quality Requirements of IMPs as applicable to clinical trials authorised under Directive 2001/20/EC

4.1 Pharmaceutical Quality System

Annex 13 *– Quality Management*

1. The Quality System, designed, set up and verified by the manufacturer or importer, should be described in written procedures available to the sponsor, taking into account the GMP principles and guidelines applicable to investigational medicinal products.

2. The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained.

➔ Comment

The importance of a Quality System is of primary importance to manufacturing IMPs as well as for commercial products. Therefore this concept is described in the first point of the guideline dedicated to the specific GMP requirement to IMPs. It is also to clarify that both EU Directive 2001/20 and Annex 13 use the term manufacturer/importer to identify the role identical to senior management in Chapter 1 of the EU GMP Guide. Furthermore, the Sponsor is introduced as the other responsible part playing a main role in the clinical trial arena.

The second point starts detailing the concept of flexibility in IMP manufacture, that is extensively addressed along with this guideline.

Annex 13 *– Personnel*

4. The **Qualified Person** should ensure that there are systems in place that meet the requirements of GMP and should have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the **Qualified Person** in connection with the certification of investigational medicinal products is given in paragraphs 38 to 41.

➔ Comment

Beside the competences already described, the QP for IMP should have experience/skills in pharmaceutical development (e.g. ICH Q8 Pharmaceutical Development) and in clinical trial processes (e.g., type of clinical studies: open, blinded, double-blinded, etc.).

4.2 Batch certification

The legal basis for the IMP batch certification is the content of the art. 13 of the EU Directive 2001/20, that is confirmed in art. 38 and 39 of Annex 13. The art. 40 gives a practical "checklist" for the GMP assessment of the batch. Detailed assessment should be carried out for the phases of packaging and labelling to assure the correct product will be administered to the patient as foreseen by the clinical protocol.

Annex 16 *- Scope*

This Annex provides guidance on the certification by a ***Qualified Person (QP)*** *and on the batch release within the European Union (EU) of medicinal products for human or veterinary use holding a marketing authorisation (MA) or made for export.*
The principles of this guidance also apply to investigational medicinal products (IMP) for human use, subject to any difference in the legal provisions and more specific guidance published by the European Commission

➔ Comment

Apart from the scope, there is no other mention of the IMP in Annex 16. It is anyway important to understand the principles and try to apply them for IMPs. This recommendation is repeated by art. 41 of Annex 13

EU Directive 2001/20

13. The Member States shall take all appropriate measures to ensure that the ***qualified person*** *referred to in Article 21 of Directive 75/319/EEC, without prejudice to his relationship with the manufacturer or importer, is responsible, in the context of the procedures referred to in Article 25 of the said Directive, for ensuring:*

a. in the case of investigational medicinal products manufactured in the Member State concerned, that each batch of medicinal products has been manufactured and checked in compliance ...the principles and guidelines of good manufacturing practice for medicinal products for human use, the product specification file and the information notified pursuant to Article 9(2) of this Directive;

b. in the case of investigational medicinal products manufactured in a third country, that each production batch has been manufactured and checked in accordancewith standards of good manufacturing practice at least equivalent to those laid down ..., in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to Article 9(2) of this Directive;

c. in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to above cannot be obtained, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information notified pursuant to Article 9(2) of this Directive.

Insofar as the provisions laid down in (a), (b) or (c) are complied with, investigational medicinal products shall not have to undergo any further checks if they are imported into another Member State together with batch release certification signed by the qualified person.

➔ Comment

In all cases, a batch of IMP must satisfy the following three criteria:

- **Compliance to EU GMP**
- **Accordance with the information reported in the Investigational Medicinal Product Dossier as approved by the Competent Authority**
- **Accordance with the Product Specification File**

Annex 13 *– Shipping*

43. Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step procedure: certification by the Qualified Person; and release by the sponsor for use in a clinical trial following fulfilment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. Both steps should be recorded and retained in the relevant trial files held by or on behalf of the sponsor. The Sponsor should ensure that the details set out in the clinical trial application and considered by the ***Qualified Person*** *are consistent with what is finally accepted by the Competent Authorities. Suitable arrangements to meet this requirement should be established. In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the* ***QP*** *and the Sponsor*

➔ **Comment**

The Qualified Person and the Sponsor have the ultimate accountability to assure the safety of the patients and the compliance with the quality specification of the IMP, therefore they must have the same set of information to affirm that a batch is suitable for that clinical trial because is, among others, compliant with the IMPD approved by the Competent Authority. A Quality Agreement must be in place between the QP and the Sponsor to manage this point. It has to underline that this is the unique point where Annex 13 demands a formal change control instead of less critical change management, as in several other paragraphs.

4.3 Non-Conformity Management

Annex 13 *- Complaints*

48. The conclusions of any investigation carried out in relation to a complaint which could arise from the quality of the product should be discussed between the manufacturer or importer and the sponsor (if different). This should involve the ***Qualified Person*** *and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and subjects.*

➔ **Comment**

Complaints due to IMP quality issues should be investigated as usual in the GMP arena, with the involvement of the QP with an overall responsibility to ascertain that there is no potential risk to the subjects participating to the clinical trial and, in coordination with the Sponsor and the Clinical Investigators, the clinical study itself is not at risk. Furthermore, as a specific competence of the QP, to check that the pharmaceutical development is scientifically justified.

Annex 13 *- Recalls*

49. Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer were different. The investigator and monitor need to understand their obligations under the retrieval procedure.

50. The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.

➔ **Comment**

Even if not mentioned in these articles, the role of the Qualified Person is fundamental to protect the safety of the patients for retrieving IMPs. Furthermore, the QP should be aware if agreements/systems are in place with the suppliers of comparators or other medications to communicate when there is a need to recall these products. In the other way, clear responsibilities should be defined to inform the manufacturer of compactors or medications is problems arise during the clinical trials with these products.

4.4 Relationship with Suppliers

Two aspects are highlighted in the supply chain of a batch of IMP: the quality of the API and the equivalence to EU GMP for the sites located in extra EU countries.

Quality of the API

Not to do: compilation of the QP declaration (EMA Guidance 196292 / 2014) on Part II compliance of the active ingredient. There is no requirement for the API used in the manufacture of IMP, but the QP, certifying the batch, should anyway verify the suitability of the API for its use in a clinical trial.

Equivalence to EU GMP

The QP must confirm that each manufacturing site (including analytical labs), listed in the IMPD, applies an equivalent EU GMP system and he/she should indicate the method which has been used for the verification (e.g., audit, documentation assessment, valid EU GMP certificate). This QP's declaration is attached to the CTA and evaluated by the Competent Authority during the approval process of the clinical trial.

4.5 Outsourcing Activities

No significant difference from commercial manufacturing.

Annex 13 *– Manufacturing and packaging at different sites*

41. Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Qualified Persons, the recommendations listed in Annex 16 to the GMP Guide should be followed as applicable.

4.6 Quality Oversight

There are circumstances during the life cycle of clinical trials where the Qualified Person is requested to keep under control the quality of the operations that are performed not under his/her direct control. A detailed Quality Agreement could be the tool t substantiate the efficient management of these tasks.

Annex 13 *- Packaging and labelling*

42. Where permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the ***Qualified Person*** *is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the* ***Qualified Person*** *in this regard.*

➔ Comment

These articles deal with critical operations for the success of a clinical trial: packaging and labelling and the conditions when they can be carried out far from a GMP authorized site but under control of skilled personnel. The QP is not accountable because there is no need to issue a certification, but – in agreement - with the Sponsor (the ultimate responsible) he/she should give "advice" (recommendation, assistance) to assure compliance of these activities with the GMP principles.

Annex 13 *- Non-investigational medicinal product*

Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial... These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator. The sponsor should ensure that they are in accordance with the notification/request for authorisation to conduct the trial and that they are of appropriate quality for the purposes of the trial taking into account the source of the materials, whether or not they are the subject of marketing authorisation and whether they have been repackaged. The advice and involvement of a ***Qualified Person*** *are recommended in this task.*

GUIDANCE *on Investigational Medicinal Products (IMPs) and 'non-Investigational Medicinal Products' (NIMPs) (rev. 1, march 2011)*

➔ Comment

This is another area where the Qualified Person should be involved by the Sponsor to give his/her pieces of advice on quality-related topics for the auxiliary products to be used in the clinical trial. The guidance requires the QP certification for NIMPs imported from third countries.

Annex 13 *- Transfers of investigational medicinal products*

47. Transfers of investigational medicinal products from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer, through, for example, trial monitoring reports and records of storage conditions at the original trial site should be reviewed as part of the assessment of the product's suitability for transfer and the advice of the ***Qualified Person*** *should be sought. The product should be returned to the manufacturer, or another authorised manufacturer, for re-labelling, if necessary, and certification by a* ***Qualified Person****. Records should be retained and full traceability ensured.*

➔ Comment

This type of transfer can happen only during a clinical trial: QP must be involved to assure the product to be transferred is still suitable because, for instance, there is no risk for blind breakage and has been stored in appropriate conditions.

ADDENDUM **2**

SHIPMENT AND DISTRIBUTION OF MEDICINAL PRODUCTS

The supply chain of medicinal products includes procurement, manufacturing, holding, supplying, importing and/or exporting. All process steps involve qualified actors, require specific licenses and the compliance with guidelines about storage, shipment and distribution. The principles of traceability and of the preservation and availability of data and their integrity are also to be applied for the correct managing of all processes.

Good Distribution Practices (GDP) guidelines have been introduced as a regulatory tool to keep the pharmaceutical supply chain under control, avoiding incurring the main risks, as they state as follows:

"GDP is that part of quality assurance which ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of the manufacturer to the pharmacy or person authorized or entitled to supply medicinal products to the public"

These guidelines require the presence of a **Responsible Person**, to whom the supervision of overall quality requirements is assigned.
In particular, the Responsible Person has to take in due count the following duties:

- general knowledge and quality supervision of procurement, selling, storage, shipping, import and export processes
- knowledge of products being distributed and their stability requirements
- application of picking and packing principles (FIFO, FEFO, ...)
- implementation of traceability requirements
- implementation of storage principles (warehouse mapping, alarms and deviations management)
- complaints, recalls and returned products management
- CAPA management
- Self-inspections and audit management
- adequate training program for the quality-related tasks of the personnel involved
- quality-related suppliers assessment, including quality and technical agreements approval
- falsified medicines management according to the FMD requirements

The Responsible Person should be contracted, depending on the size of the operations to be handled by the wholesale. The Responsible Person should demonstrate his/her abilityto supervise overall quality requirements and the storage conditions impacts on the dosage forms handled by the wholesaler.

Responsible Person can delegate to a deputy his duties, not his/her responsibilities. Duties of the deputy should be listed and recorded preferably in a Job Description or in an SOP.
A matrix of responsibilities should be present to identify and address the delegated tasks, keeping always the responsibility on the shoulders of the Responsible Person.

The Responsible Person approach and conduct must be driven by the main risks to be considered in the specific supply chain of medicines.
The main risks to manage and to mitigate are represented by the following features:

- Supply Continuity and Traceability
- Vendors Qualification
- Compliance Issues Management
- Second Tier Suppliers Management
- Pest Control Management
- Temperature Control and monitoring in Warehousing and in transportation
- Change Control Management
- Fraudulent Activities assessment in the Supply Chain Management

In the following paragraphs, the main requirements of the current EU GDP guidelines **(2013/C 343/01)** are reported together with some comments for their implementation.

Chapter 1- Quality Management

Wholesale distributors must maintain a quality system setting out responsibilities, processes and risk management principles in relation to their activities. All distribution activities should be clearly defined and systematically reviewed. All critical steps of distribution processes and significant changes should be justified and where relevant validated. The quality system is the responsibility of the organization's management and requires their leadership and active participation and should be supported by staff commitment.

Key Concepts

✔ Organization chart, with reference to processes and procedures
✔ Documented Quality System, monitoring its effectiveness
✔ Identification of the Quality Assurance Manager and appointment of a Responsible Person
✔ Presence of competent personnel and adequate material resources
✔ Need to take appropriate corrective actions when requested (CAPA plans)
✔ Control and verification of management of outsourced activities
✔ Monitoring and periodic verification of the Quality System
✔ Evaluation and Management of Risks

➔ Comment

As per the GMP rules, in GDPs the actors of the shipment and distribution must put in place a robust and well-documented quality system, able to provide a clear picture of the full process detailing all the activities performed, specifying responsibilities and training of the involved personnel.

Proper infrastructures (buildings and rooms, devices to control and continuously monitor temperatures and related alarms, adequate means of transport) are requested. Particular emphasis must be put in the management of the traceability of the goods with proper instruments (bar-codes readers, data files repository and computerized system complying with Annex 11 of GMP guidelines).

A risk analysis must be applied to define existing gaps with GDP requirements and to put in place a remediation plan with corrective and preventive actions able to mitigate each residual risk in the supply and distribution chain of medicines.

The Responsible Person should be involved in any change having GDP and regulatory impact and in the management review meetings when quality system effectiveness should be discussed, evaluated, reviewed and approved.

Overall accountability and accuracy of quality records are under the full responsibility of the Responsible Person.

Chapter 2 - Personnel

The correct distribution of medicinal products relies upon people. For this reason, there must be sufficient competent personnel to carry out all the tasks for which the wholesale distributor is responsible. Individual responsibilities should be clearly understood by the staff and be recorded.

Key Concepts

- Responsible Person
  - ✔ Adequate competencies and experience (professional profile)
  - ✔ Well defined responsibilities in a job description, including the time of presence
  - ✔ Guarantor of the Quality Management System implementation, in full compliance with GDPs

- Other staff
  - ✔ Personnel competence and adequacy of the number to the needs
  - ✔ Clear and defined responsibilities (Job Descriptions)

- Training
  - ✔ Continued, documented and adapted to the needsComment

➔ Comment

A clear definition of the roles and responsibilities of the key personnel must be primary defined and reported in job descriptions, to ensure the adequacy of the people in each operation carried out by the wholesaler.

Performances should be periodically assessed by using key indicators and bydocumented interviews to ascertain the proper knowledge of the whole process and its impact on the interfaces.

The Responsible Person should establish and approve Job Descriptions, training plans and also conduct training sessions.

Chapter 3 – Premises and Equipment

Wholesale distributors must have suitable and adequate premises, installations and equipment, so as to ensure proper storage and distribution of medicinal products. In particular, the premises should be clean, dry and maintained within acceptable temperature limits.

Key Concepts

✔ Rooms suitable for maintaining the required storage conditions
✔ Rooms with segregated areas for particular categories of medicinal products (returned)
✔ Access allowed only to authorized personnel
✔ Special rooms for handling dangerous drugs
✔ Rooms cleaned and protected from insects, rodents and flying animals
✔ Rest and refreshment areas separated from storage areas
✔ Suitable instrumentation, validated and calibrated, for temperature management
✔ Validated information systems to support distribution processes
✔ Qualification of any installed equipment
✔ Periodic review of validation and appropriate management of changes

➔ Comment

Premises and equipment are important subsidies in the shipment and distribution: they are strongly requested to properly manage the activities and ensure the requested storage and distribution conditions.

Chapter 4 - Documentation

Good documentation constitutes an essential part of the quality system. Written documentation should prevent errors from spoken communication and permits the tracking of relevant operations during the distribution of medicinal products.

Key Concepts

✔ Appropriate document management of procedures, operating instructions, data
✔ Clear documentation accessible to the personnel in charge
✔ Approved, signed and dated documents
✔ Change to properly managed and approved documentation
✔ Documentation kept for at least 5 years
✔ Appropriate management of electronic documentation

➔ Comment

Good documentation practices must be put in place before starting any activity having an impact on the efficacy, safety and quality of the medicines stored and shipped at each level of the supply chain. All the activities must be detailed in written and preliminarily approved SOPS and duly recorded to ensure the full traceability of each operation and data collection.

Chapter 5 - Operations

All actions taken by wholesale distributors should ensure that the identity of the medicinal product is not lost and that the wholesale distribution of medicinal products is performed according to the information on the outer packaging.

The wholesale distributor should use all means available to minimize the risk of falsified medicinal products entering the legal supply chain.

All medicinal products distributed in the EU by a wholesale distributor must be covered by a marketing authorization granted by the EU or by a Member State.

Any distributor, other than the marketing authorization holder, who imports a medicinal product from another Member State must notify the marketing authorization holder and the competent authority in the Member State to which the medicinal product will be imported of their intention to import that product.

All key operations described below should be fully described in the quality system inappropriate documentation.

Key Concepts

✔ Distribution authorization
✔ Supplier qualification and surveillance on suitability, competence and reliability
✔ Qualification of customers and verification of their eligibility for purchase
✔ Storage of medicines: hygiene, safety, temperature, expiry dates.
✔ Destruction of obsolete drugs
✔ Preparation of shipping orders
✔ Exports

➔ Comment

Any operation must be conducted following standard operating procedures and recorded to allow traceability, to prevent the risk of falsified medicinal product entering in the supply chain and to ensure that medicines are handled in proper conditions of storage (hygiene, temperature, safety, expiry date).

Any actor of the supply chain should be easily identified through the related marketing authorization

Chapter 6 – Complaints, Returns, Falsified Medicinal Products and Medicinal Products Recalls

All complaints, returns, suspected falsified medicinal products and recalls must be recorded and handled carefully according to written procedures. Records should be made available to the competent authorities.

An assessment of returned medicinal products should be performed before any approval for resale. A consistent approach by all partners in the supply chain is required in order to be successful in the fight against falsified medicinal products.

Key Concepts

✔ Adequate records of returned medicines recalled, presumed falsified
✔ Correct management of complaints with MAH involvement
✔ CAPA plans, where necessary
✔ Correct returns management and "risk management" when necessary
✔ Particular surveillance on " suspects of falsified medicines"
✔ Adequate recall management procedures

➔ Comment

Complaints, returns and recalls are very critical aspects that should be promptly managed to allow the adequate reactivity of the whole supply chain. A critical aspect to be taken in proper consideration is the communication between the different actors of the supply chain, including the manufacturing authorization holder.

Equally critical is the documentation (SOPs and records) and the training associated with the management of the complaints and recalls.

The criteria for final disposition of products involved in a complaint, return or recall process should be defined in order to make the decision based on a documented and justified manner. In particular, the criteria to accept returned products to saleable stock should be defined in advance in a written document (normally in the Quality Agreement or in a procedure) in order to support the final decision after checks.

The Quality Agreement should detail the responsibilities for receiving, investigating and reporting complaints involving if requested, the Manufacturing Authorization Holder, especially for adverse reactions and pharmacovigilance issues.

Periodical mock recalls are requested to be performed in order to check the ability of the system to adequately react to a real event and to improve its preparedness.

The Responsible Person plays a key role in recall operations having the main duty to coordinate connections between the company, suppliers and customers and Regulatory Bodies involved.

Chapter 7 – Outsourced activities

Any activity covered by the GDP guide that is outsourced should be correctly defined, agreed and controlled in order to avoid misunderstandings which could affect the integrity of the product. There must be a written contract between the contract giver and the contract acceptor which clearly establishes the duties of each party.

Key Concepts

✔ Not "deformability" of the responsibility to the subcontractor
✔ Need to transfer all the necessary know-how to the operator
✔ Need for the contractor to have adequate staff and facilities
✔ The necessity for the subcontractor to transfer the necessary information to the contractor

➔ Comment

As well as for the GMPs, the outsourced activities remain under the responsibility of the Contract Giver. A clear and well-defined Quality and Technical Agreement must be put in place between the parties before starting any activity.

It is important to transfer the Contract Acceptor the complete knowledge of the transferred activities and their criticalities. It is also essential to verify, through an audit, the adequacy of the Contract Acceptor in terms of premises, personnel, documentation.

The Responsible Person should establish a monitoring program to ensure thecompliance of each contractor through audits and periodic assessment of their quality performances and issues.

The Responsible Person is requested to have an updated knowledge of the contractors' regulatory status in order to promptly intervene in considering any non-compliance issue: audits, periodically conducted, should be the opportunity to verify the full compliance of all contractors.

Chapter 8 – Self-Inspections

Self-inspections should be conducted in order to monitor implementation and compliance with GDP principles and to propose necessary corrective measures.

Key Concepts

✔ Define frequency and identify appropriate team
✔ Carry out the inspection in an impartial and detailed manner
✔ Record all the self-inspections and the non-conformities found
✔ Draw up a remediation plan and verify its adequacy and realization

➔ Comment

Routine self-inspections should be conducted in order to verify the adequacy of the quality system and its continuous improvement.

An adequate CAPA plan management must be in place to guarantee the remediation plan execution and to verify the efficacy of the actions as implemented.

The Responsible Person should plan a periodic self-inspection in which the frequency is supported by the risk assessment approach

Chapter 9 - Transportation

It is the responsibility of the supplying wholesale distributor to protect medicinal products against breakage, adulteration and theft, and to ensure that temperature conditions are maintained within acceptable limits during transport.

Regardless of the mode of transport, it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity. A risk-based approach should be utilized when planning transportation.

Key Concepts

✔ Also if depending on the supply agreement, normally the contractor of the transport is responsible for its correct execution
✔ Adequacy of the means, hygiene, respect for temperature are fundamental
✔ The evidence of the registration of the temperature is a critical element to verify
✔ Recording instrumentation needs periodic calibration and all calibration and registration data must be accessible
✔ In the case of "cool packs", suitable procedures and controls must be defined

➔ Comment

Transportation is a keyword in the shipment and distribution process. Means of transport must be adequate to ensure temperature conditions maintaining and recording through appropriated and calibrated devices and infrastructure and to avoid any damage or adulteration of the goods.

Drivers should be trained to understand the impact and criticality of their work especially for products requiring special storage conditions during

transportation.
Appropriated checks and recording should be established at the moment that the goods leave a place and reach the destination.

Chapter 10 – Specific Provisions for Brokers

Principle A 'broker' is a person involved in activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that does not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.

Brokers are subject to a registration requirement. They must have a permanent address and contact details in the Member State where they are registered. They must notify the competent authority of any changes to those details without unnecessary delay. By definition, brokers do not procure, supply or hold medicines. Therefore, requirements for premises, installations and equipment as set out in Directive 2001/83/EC do not apply. However, all other rules in Directive 2001/83/EC that apply to wholesale distributors also apply to brokers.

Key Concepts

✔ The broker operates in the commercial field and does not physically manage the drug
✔ The broker must be "registered" as such and then be authorized
✔ The broker must have an adequate Quality System in place
✔ Knowledge of relevant EU legislation on drugs and falsified medicines is required
✔ The broker must be able to handle any claims and fakes

➔ Comment

Brokering is a step of medicinal products supply chain process, where there is no physical involvement of the products. However, any broker operation has to be recorded, to meet traceability requirements.

Brokers have the duty to assess the adequacy of the parties involved, like outsourced activities in order to verify the compliance with the main aspects of GDPs that brokers could manage in advance also through a remote audit.

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