EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 January 2020
EMA/457570/2019
GMP/GDP Inspectors Working Group

Reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders

Draft

Draft agreed by GMP/GDP Inspectors Working Group	June 2019
Adopted by GMP/GDP Inspectors Working Group for release for consultation	June 2019
Start of public consultation	17 January 2020
End of consultation (deadline for comments)	17 April 2020

Comments should be provided using this template. The completed comments form should be sent to adm-gmdp@ema.europa.eu

Keywords	Good Manufacturing Practice, GMP, Marketing Authorisation Holder, MAH

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Table of contents

1. Introduction and purpose

This Reflection Paper is focussed on the GMP-related responsibilities that apply to Marketing Authorisation Holder (MAH) companies. While it is recognised that many MAH companies are not directly engaged in the manufacture of medicinal products themselves, the current European Commission (EC) guide to GMP (hereafter referred to as the 'GMP guide') refers, in several places, to MAHs and their responsibilities in relation to GMP.

In general, these responsibilities relate to outsourcing and technical agreements, that require the MAH to perform certain specific tasks (e.g. evaluating the results of product quality reviews, agreeing irradiation cycles with manufacturers, etc.). These responsibilities are spread over the various chapters and annexes of the GMP guide, and are quite numerous.

This Reflection Paper seeks to provide clarity as to what the various responsibilities are and what they mean for MAHs at a practical level. In addition to the MAH responsibilities in the GMP guide, this paper also addresses the various legislative provisions (i.e. in European Directives and in other guidelines) which relate to GMP and which concern MAHs. Some of the responsibilities stated in the legislation (e.g. in Directives 2001/83/EC and 2001/82/EC) and in applicable guidelines are written in a way that they apply to marketing authorisation applicants, and they are included in this Reflection Paper because those provisions also convey responsibilities upon marketing authorisation holders in the post-authorisation phase.

It should be noted that, as indicated in Annex 16 of the GMP guide, the ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the MAH. It is also important to note that, while certain activities of an MAH may be delegated to a manufacturer or other party, the MAH retains the responsibilities which are outlined in this paper. The GMP guide also does not provide for *reduced* MAH responsibilities (or for the *delegation* of responsibilities) in situations where the MAH and the manufacturer belong to the same overall group of companies but where the two companies are different legal entities. There is no difference in the responsibilities that apply to the MAH in this situation relative to when the MAH and the manufacturer are from separate and unrelated companies.

While relevant activities pertaining to the GMP-related responsibilities held by MAHs may be delegated by the MAH to its representative (if there is one) in a member state, none of the responsibilities may be delegated to that person. (Note: The representative of the MAH, commonly known as the local representative, is the person designated by the MAH to represent him in the Member State concerned. (Ref. Part 18a of Article 1 in Directive 2001/83/EC and Part 17a of Article 1 of Directive 2001/82/EC).

It is recognised that, while MAHs have a significant role in facilitating GMP and MA compliance, their responsibilities in this area can, in some cases, be difficult to comprehend when reading the GMP guide or the applicable legislation. Notwithstanding this, such responsibilities are there and may be inferred. This Reflection Paper seeks to provide clarity on these.

All of the references currently in the GMP guide (as of April 2019) that relate to MAH responsibilities are discussed in this Reflection Paper. This paper, however, should not be taken to provide an exhaustive list of those references on an ongoing basis. Rather, it sets out the general GMP-related responsibilities and activities of the MAH, and it presents them under a number of different *themes*. These themes are outlined below in Section 5. MAH companies should have a system in place to ensure that they remain up-to-date with current GMP requirements and updates thereafter.

Where possible, the text within each theme provides an explanation of what the various responsibilities may mean at a practical level for MAHs; guidance is also given on what is expected of an MAH when

fulfilling that responsibility. It should be noted, however, that this Reflection Paper does not provide guidance on 'how' the various responsibilities might be fulfilled.

Article 111 of Directive 2001/83/EC and Article 80 Directive 2001/82/EC give powers to member state authorities to inspect the premises of MAH companies; this includes situations in which there are grounds for suspecting non-compliance with the legal requirements laid down in the Directives, including with the principles and guidelines of GMP. When such inspections are carried out, this Reflection Paper may serve as useful guidance for the competent authorities performing the inspections.

2. Scope

The Reflection Paper concerns the responsibilities and activities of MAHs with respect to the European Commission's guide to GMP (Parts I, II, and its relevant Annexes) for medicines for human and veterinary use.

The scope also extends to certain legislative provisions that have relevance to GMP, such as those stated in the GMP Directives 2003/94/EC and 92/412/EC (as amended), as well as relevant articles in Directive 2001/83/EC and Directive 2001/82/EC.

When referring to manufacturers and manufacturing sites, the Reflection Paper is referring to any site engaged in manufacturing and related activities (e.g. contract analysis) that are subject to EU GMP requirements. This includes contract testing facilities whether listed in the MA (e.g. laboratories performing batch release testing) or not (e.g. laboratories performing ongoing stability testing).

This Reflection Paper is focussed on the GMP-related responsibilities that apply to all MAH companies, including **Registration Holder (RH) and Traditional-use Registration Holder (TRH) companies**. When this paper makes reference to the responsibilities and activities of the MAH, it is understood that the principles are equally applicable to the RH and TRH.

FMD: The relevant provisions of the Falsified Medicines Directive 2011/62/EU and the related Delegated Regulations (including the Safety Features Regulation 2016/161) are also within scope of this Reflection Paper.

ATMPs: The principles set out in this paper also generally apply to MAHs of ATMPs. However, the specific provisions of Part IV of the GMP guide are not specifically discussed here, and there are certain specific requirements that apply to ATMPs, as stated in Part IV (such as a 30 year data retention requirement) that differ from what is set out in this Reflection Paper.

GDP Responsibilities: While this Reflection Paper is not intended to address the GDP-related responsibilities that may apply to MAHs, it is considered important to highlight here that MAHs do need to understand the type of interfaces that may need to be in place with the wholesalers they employ or engage. For example, current EU GDP guidelines require that medicines wholesalers notify the MAH of certain information, e.g. information concerning falsified products and quality defects (Ref. EU GDP Guidelines, 2013, Sections 6.2 and 6.4). As a result, it is considered that MAHs should have systems in place to accept and act upon such information from the wholesale distribution chain when received.

The Reflection Paper does not extend to other MAH responsibilities and activities that may be set-out in other official guidance documents and legislation, such as those relating to other GxP areas, pharmacovigilance, etc.

3. How this Reflection Paper sets out the various MAH responsibilities

In section 5 of this paper, each GMP requirement that applies to the MAH is outlined, with its key message stated or summarised.

- This is then followed by the exact text that is in the GMP guide (or in applicable legislation or in other guidelines) on this point. In some cases, the exact text is presented between quotation marks;
- A clear reference to the relevant part of the GMP guide or the applicable legislation is then stated;
- Where possible, an explanation of what the requirement means at a practical level for the MAH is provided, in italics.

4. The role of the MAH in facilitating compliance with GMP and the Marketing Authorisation (MA)

As noted above, MAHs have an important role in facilitating compliance with GMP and the MA; this is reflected in the multiple references to MAH responsibilities that are in the GMP guide. These responsibilities generally relate to:

- The provision of information by the MAH to competent authorities, manufacturing sites and Qualified Persons;
- The collation of quality-related information from different actors in the manufacturing and distribution chain.

Evidence of GMP compliance: When submitting a new application for an MA, the applicant has the responsibility to make sure that the proposed manufacturers hold a valid MIA, a valid GMP Certificate (or equivalent). In the same way, during the life-cycle of a product, the MAH must ensure that the manufacturers are authorised and compliant with GMP.

Abbreviated version of CTD module 3: In the introductory chapter to the GMP guide, it is stated that "Throughout the Guide, it is assumed that the requirements of the Marketing Authorisation relating to the safety, quality and efficacy of the products, are systematically incorporated into all the manufacturing, control and release for sale arrangements of the holder of the Manufacturing Authorisation." This implies that the MAH has a responsibility to communicate what is registered in the MA to the manufacturing sites. In doing this, MAHs sometimes prepare abbreviated versions of CTD module 3 of the MA for use by the manufacturing sites and QPs; this is considered acceptable; as long as those abbreviated versions are sufficiently comprehensive and are subject to formal change control and oversight activities.

Labelling and product information: Care should also be taken to ensure that, what is registered in CTD module 1 of the dossier in relation to the approved product labelling (including the package leaflet) and changes to same are communicated to the manufacturer in a timeframe which will enable the manufacturer to ensure that all batches it produces have the correct labelling and product information.

Chapter 7 and MAHs: While Chapter 7 is primarily intended to deal with "the responsibilities of manufacturers towards the Competent Authorities of the Member States with respect to the granting of marketing and manufacturing authorisations" (Ref. Chapter 7, Principle), it is also directly relevant to MAHs, as indicated by paragraph 7.3. This states: "Where the marketing authorisation holder and the

manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter." (Ref. Chapter 7, Paragraph 7.3).

MA variations: The need to provide the relevant manufacturing sites with the necessary information about MA variation approval and target implementation dates is considered another important responsibility for the MAH. It is a key activity which enables those sites to ensure that future batches of the product, which may be QP-certified after a certain date, comply with the varied MA. This responsibility may be inferred from Chapter 7 of the GMP guide, in relation to Outsourced Activities, which states:

> "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." (Ref. Chapter 7, Paragraph 7.6).

Regulatory commitments: The management of regulatory commitments (which are often made between an MAH and a competent authority) is another area that can have a significant impact upon MA compliance generally, if it is not under an appropriate level of control by the MAH. This is especially the case in relation to the communication of such commitments to the manufacturing sites by the MAH; thus, the importance of robust communication processes is highlighted in this Reflection Paper. Indeed, the management of regulatory commitments may assume increased importance in the coming years, given that the regulatory environment may move towards greater flexibility in the area of post-approval change management, via ICH Q12, related to medicinal products for human use. Such flexibility is likely to rely on the effectiveness of the pharmaceutical quality system that is in place, as this will help assure regulatory compliance in the implementation of such post-approval changes. MAHs may have an important role in this area.

Two-way communication systems: MAHs can facilitate compliance by establishing robust two-way communication systems with national competent authorities, manufacturing sites, Qualified Persons (QPs), and any organisations relevant to the monitoring of post-marketing quality (e.g. complaints processing and on-going stability monitoring). Doing so can help ensure that:

- The MAHs have adequate knowledge of the details of the manufacturing processes and their related controls at the finished product and active substance manufacturing sites, including situations where there are Active Substance Master Files (ASMFs) and Certificates of the European Pharmacopoeia (CEPs) in place.
- The manufacturing sites and QPs have visibility of what is registered in the marketing authorisation and what, if any, regulatory commitments have been agreed with the competent authorities;
- The MAHs are adequately informed of change management activities at the manufacturing sites, particularly in relation to changes which may impact upon modules 1, 2 and 3 of the MA as well as on the contents of ASMFs and CEPs. This can help ensure that the MAHs are involved in regulatory impact assessments for relevant change proposals and that any necessary notifications or variation applications are made to the competent authorities.

Data integrity: This is another area of relevance to MAHs; it can result in GMP non-compliances if there are not robust control systems to assure the integrity of data pertaining to the MA, which may be used or required by the manufacturers. Thus, it is considered that MAHs should have systems in place to ensure the integrity and reliability of the data that are used to discharge their responsibilities. There should be assurance that product lifecycle data relating to GMP activities, including relevant MA variations, are reliable, complete and accurate. The MAH should also ensure the long term security and archiving of the data upon which the MA relies.

Compliance management process: MAHs should be aware of the 'Compliance Management' process that has been put in place within the EEA; this is used in situations where a manufacturing site has been found to be on the border between achieving a minimum level of GMP compliance and serious GMP non-compliance. MAHs should be aware of their ability to facilitate compliance, and may find that their involvement in the remediation of such issues is necessary.

Non-compliance with MAH obligations: Based on Article 116 of Directive 2001/83/EC, a MA for which the MAH does not fulfil its various obligations may be suspended, revoked or varied by the competent authority. It states that an authorisation shall be "suspended, revoked, withdrawn or varied where the particulars supporting the application as provided for in Article 8 or Articles 10, 10a, 10b, 10c and 11 are incorrect or have not been amended in accordance with Article 23, or where the controls referred to in Article 112 have not been carried out."

5. Areas of the EC guide to GMP that relate to MAHs

As noted in the Introduction, there are various references within the GMP guide to MAH-related responsibilities. These span a number of different chapters and annexes, and in this Reflection Paper, they are grouped together under a number of different themes. These are set out below. While there is some duplication across the different themes, it is considered helpful to consider the responsibilities and activities in this way.

A number of the legislative provisions that exist within EU medicines legislation which concern the GMP-related responsibilities of MAHs are also included within the various themes, where relevant. The themes are:

- Outsourcing and technical agreements;
- Audits and qualification activities;
- Communication with manufacturing sites (e.g. MA dossier information, variations, regulatory commitments, etc.);
- Product Quality Reviews;
- Quality defects, complaints and product recalls;
- Maintenance of supply of medicinal products;
- Continual improvement activities.

(Note that FMD-related responsibilities are discussed in Chapter 6).

5.1. Outsourcing and technical agreements

This section discusses the various MAH responsibilities which apply to outsourced activities and technical agreements. Section 5.2 below, relating to Audits and Qualification, is also relevant here and its contents should be noted.

See also section 5.3 below in relation to the importance of a technical agreement being in place between the MAH and manufacturer when they are different legal entities. That section also addresses the merits of having a technical agreement in place between the MAH and the active substance manufacturer to address certain communication requirements in relation to situations in which there is an Active Substance Master File (ASMF) or a CEP registered for a MA.

5.1.1. Delegation of activities

As noted earlier in this Reflection Paper, there is no provision within the GMP guide or in applicable legislation for the delegation of responsibilities by an MAH to other parties. However, there may be delegation of the tasks and activities which relate to those responsibilities, and this is relevant to the topic of outsourcing. It is considered that any such delegation should be described in writing and agreed by the relevant parties.

In general terms, it is the responsibility of the MAH to ensure that the person or entity, to whom any task or activity has been delegated, possesses the required competence, information and knowledge to successfully carry out the outsourced activities (Ref: GMP guide Chapter 7, Paragraphs 7.5 and 7.6). Special attention should be given to situations where tasks have been delegated in a fragmented way - to more than one party – as applying oversight of multiple parties can be a challenge in the life-cycle management of the medicinal product.

5.1.2. Documenting outsourced activities

There are obligations to ensure that outsourced activities are described in writing. Chapter 7 of the GMP guide requires that "any activity that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality." (Ref: GMP guide Chapter 7, Principle).

Chapter 7 of the GMP guide also states that "Where the marketing authorisation holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter." (Ref. Chapter 7, Paragraph 7.3). In practice there are various scenarios that may apply. For example, the two parties may be different legal entities within the same company group, or they may be unrelated companies. Regardless of such scenarios, it is considered that the arrangements between the parties should be documented in technical agreements.

Where an MAH is engaged in an outsourcing activity, the above means that the MAH should agree in writing what exactly the activity is, and how it will be controlled.

5.1.3. Compliance with the Marketing Authorisation

If an outsourced activity is one that may affect compliance with the MA, there should be controls in place which provide assurance that the requirements of the MA are complied with. This also has relevance in relation to activities concerning post-approval changes and their implementation.

The GMP guide states that "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." (Ref. Chapter 7, Paragraph 7.2)

Chapter 1 of the GMP guide states that "Where manufacture is outsourced, the technical agreement between MAH and manufacturer should address the respective responsibilities in producing and evaluating the product quality review." (Ref. Chapter 1, Paragraph 1.11). *This means that the manufacturer may be responsible for compiling and evaluating certain elements of the PQR, while the MAH may be responsible for compiling and evaluating other parts of the PQR. (See below and also section 5.4 for further information in relation to PQRs). It is noted that PQRs contain information in relation to the MA, in terms of variations, post-approval commitments, etc.*

5.1.4. Document retention

There are certain document retention requirements stated in the GMP guide which are important from the perspective of the MAH, as they support the MA and documentation retention activities may be the subject of outsourcing.

It is considered that, while document retention activities may be delegated (i.e. outsourced) to the manufacturer, the MAH remains responsible for these. Chapter 4 of the GMP guide provides useful guidance relating to the storage and retention requirements of documentation. It states that "…the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation should be retained whilst the authorisation remains in force." (Ref. Chapter 4, Paragraph 4.12).

While the above paragraph is aimed at the manufacturer and does not convey a direct responsibility on the MAH, it is important that the MAH be satisfied with the documentation retention policies and practices that are in place at the manufacturer, and it is considered that this area should be addressed in any outsourcing arrangement, via a technical agreement or a contract between the parties, whichever may apply.

The above paragraph goes on to state that:

> "It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise."

Again, the above text is very relevant for the MAH, as validation data and reports, and stability reports are key elements of the documentation needed to support an MA.

The GMP Directive 2003/94/EC, places a direct responsibility on the MAH with respect to the retention of documentation. In relation to investigational medicinal products, it requires the batch documentation to:

> "… be retained for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. The sponsor or marketing authorisation holder, if different, shall be responsible for ensuring that records are retained as required for marketing authorisation in accordance with the Annex I to Directive 2001/83/EC, if required for a subsequent marketing authorisation" (Ref. Directive 2003/94/EC, Article 9).

Please note that this requirement is not stated in Directive 2017/1572 which will replace Directive 2003/94/EC.

It is considered that the above record retention responsibilities be agreed in a technical agreement between the manufacturer, MAH or sponsor. The EMA Guideline EMA/202679/2018 (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) also provides useful information in this regard.

5.1.5. Technical agreements in relation to Product Quality Reviews (PQRs)

Chapter 1 of the GMP guide states that "Where manufacture is outsourced, the technical agreement between MAH and manufacturer should address the respective responsibilities in producing and evaluating the product quality review." (Ref. Chapter 1, Paragraph 1.11). *This means that the manufacturer may be responsible for compiling and evaluating certain elements of the PQR, while the MAH may be responsible for compiling and evaluating other parts of the PQR. (See Section 5.4 below for further information in relation to PQRs).*

5.1.6. Technical agreements in relation to the manufacture of biological active substances and medicinal products for human use

In relation to the manufacture of biological active substances and medicinal products for human use, there is a responsibility on the MAH to have a technical agreement in place with other parties which describes its responsibilities relating to the sourcing of human derived starting materials for biological products. The GMP guide states that for human tissues and cells used as starting materials for biological medicinal products, "a technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue establishment, Sponsors, MA Holder) which defines the tasks of each party, including the RP [Responsible Person] and Qualified Person" (Ref. Annex 2, Paragraph 36(g)).

5.1.7. Technical agreements in relation to the use of ionising radiation in the manufacture of medicinal products

In relation to the use of ionising radiation in the manufacture of medicinal products, there are certain responsibilities for the MAH documented in Annex 12 of the GMP guide.

One is a responsibility for the MAH to agree the design of irradiation cycles with the manufacturer, and another is to agree how and where irradiation cycle records are retained. The guide states that:

> "When the required radiation dose is by design given during more than one exposure or passage through the plant, this should be with the agreement of the holder of the marketing authorisation and occur within a predetermined time period. Unplanned interruptions during irradiation should be notified to the holder of the marketing authorisation if this extends the irradiation process beyond a previously agreed period." (Ref. Annex 12, Paragraph 33).

Annex 12 also states that:

> "Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and retained. The method and place of retention should be agreed between the plant operator and the holder of the marketing authorisation." (Ref. Annex 12, Paragraph 44).

Annex 12 also requires the MAH of a product which includes ionising radiation in its processing to refer to the CPMP guidance on "Ionising radiation in the manufacture of medicinal products" (Ref. Annex 12, Note).

Some of the above responsibilities in Annex 12 are quite technical in nature, and they require the MAH to be in a position to understand and to technically assess the design of irradiation cycles.

The direct requirement for the MAH to work with the manufacturer with regard to the design of irradiation cycles is not considered a task that may be delegated by the MAH to the manufacturer.

However, the records retention tasks are considered ones that may be delegated to the manufacturer, and thus may be the subject of outsourcing arrangements.

5.1.8. Arrangements in relation to reference and retention samples

There is an Annex in the GMP guide that provides guidance in relation to reference and retention samples. This is Annex 19, and it states certain responsibilities for the MAH in this area, mainly in relation to agreeing with the relevant manufacturers the arrangements for the taking and storage of reference and retention samples.

In the section titled 'Written Agreements' in Annex 19, the following is stated:

> "Where the marketing authorisation holder is not the same legal entity as the site(s) responsible for batch release within the EEA, the responsibility for taking and storage of reference/retention samples should be defined in a written agreement between the two parties in accordance with Chapter 7 of the EC guide to Good Manufacturing Practice. This applies also where any manufacturing or batch release activity is carried out at a site other than that with overall responsibility for the batch on the EEA market and the arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement." (Ref. Annex 19, Paragraph 6.1)

Annex 19 also addresses situations involving the closedown of a manufacturer and how reference and retention samples are to be managed. It states that:

> "If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The Marketing Authorisation holder (MAH) is responsible for such delegation and for the provision of all necessary information to the Competent Authority. In addition, the MAH should, in relation to the suitability of the proposed arrangements for storage of reference and retention samples, consult with the competent authority of each Member State in which any unexpired batch has been placed on the market." (Ref. Annex 19, Paragraph 10.2).

While the taking and storage of reference and retention samples has often been regarded as purely a manufacturing activity, it is clear from the above that the MAH has very clear responsibilities in his area also.

5.2. Audits & qualification activities

There are references to GMP audits within the European medicines legislation which have implications for applicants for MAs as well as for the corresponding MAHs. There is also a need for finished product manufacturers to be suitably qualified in order to be able to verify, for the applicant and the MAH, the GMP compliance status of the active substance manufacturer(s), as required in legislation.

5.2.1. QP declarations regarding GMP compliance status of the active substance manufacturer

Article 8(3)(ha) of Directive 2001/83/EC, for example, places a legal obligation on the applicant to provide information in the MA application concerning the GMP compliance status of the manufacturer of the active substance, and in this regard, reference is made to audits of that manufacturer. This article requires the applicant to provide "A written confirmation [QP Declaration] that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance, with [the]

principles and guidelines of good manufacturing practice by conducting audits, in accordance with point (f) of Article 46."

> Article 46 relates to the obligations that are placed upon the holder of the manufacturing authorisation, and sub-point (f) requires the finished product manufacturer "to use only active substances, which have been manufactured in accordance with good manufacturing practice for active substances and distributed in accordance with good distribution practices for active substances."

Article 8(3)(ha) goes on to state that the written confirmation submitted by the applicant "shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice."

The above means that the MA applicant has a responsibility to confirm that such audits have been carried out prior to the submission of the MA application, and to be satisfied with the GMP compliance status of the manufacturer of the active substance, as determined by the holder of the medicinal product manufacturing authorisation. It is considered that the above confirmation should be made in the form of the so-called 'QP Declaration'.

Although there is no equivalent article in Directive 2001/82/EC, in relation to medicinal products for veterinary use, a QP Declaration based on an audit is also expected for medicinal products for veterinary use.

The above responsibility to confirm to the competent authority the GMP status of the active substance manufacturer continues into the post-authorisation phase of the medicinal product, and it is the MAH that bears this responsibility. In this regard:

- GMP audits of the manufacturer are again required – such audits are referred to in the guidelines concerning MA variations (Ref. EC Guidelines 2013/C 223/01);
- In the section dealing with Administrative Changes, these guidelines place a responsibility on the MAH to submit a Type 1A variation application in relation to changes in the date of the audit to verify GMP compliance of the manufacturer of the active substance;
- The MAH is required to provide a "written confirmation from the manufacturer of the finished product stating verification of compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practices" (Ref. Administrative Change A.8). Note that a variation application is not needed when the information has been otherwise transmitted to the authorities (e.g. through a QP declaration).

The document titled 'Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture', dated 21 May 2014, also addresses the responsibility of the MAH to ensure that a written confirmation of compliance of the manufacturer of the active substance with GMP is provided to the competent authority. This document also indicates that such confirmations of compliance should be based on audits; it states that "Audits of each site for GMP compliance should be undertaken at regular intervals, normally within three years. Justification should be provided if the date since the last audit exceeds this period."

- *Use of the QP declaration template facilitates the provision of the required audit-related information by the MAH;*
- *The audit reports should be readily available and shared with the authorities, if requested;*
- *The above variation (or QP declaration) requirement relates to the fact that the GMP compliance status of the active substance manufacturer is expected to be confirmed by the manufacturer of the finished product and transmitted to the MAH, and that such confirmations (declarations) are*

based on audits carried out by, or on behalf of, the manufacturer of the finish product, as required by Article 46(f) of Directive 2001/83/EC.

5.3. Communication with manufacturing sites and competent authorities (e.g. MA dossier information, variations, regulatory commitments, etc.)

5.3.1. The need for two-way communication systems

As noted earlier in this paper, the introductory chapter to the GMP guide refers to the need for "the requirements of the Marketing Authorisation, relating to the safety, quality and efficacy of the product", to be "systematically incorporated into all the manufacturing, control and release for sale arrangements of the holder of the Manufacturing Authorisation". *This implies the need for cooperation between the MAH and manufacturer, and the need for two-way communication systems to be in place between them, particularly in relation to what is registered in the MA.*

Likewise, the so called 'GMP Directive' 2003/94/EC requires the manufacturer to ensure that "all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for marketing authorisation as accepted by the competent authorities". (Ref. Directive 2003/94/EC, Article 5).

It is reasonable to take the view that manufacturers cannot comply with the GMP requirement for batches to be in line with the relevant MA unless the MAH communicates to them what is registered in the dossier. A similar point is made in the preamble to the forthcoming new GMP Directive 2017/1572. This will replace Directive 2003/94/EC, when EU regulation 536/2014 on Clinical Trials enters into application, and it states the following:

> "All medicinal products for human use manufactured or imported into the Union, including medicinal products intended for export, should be manufactured in accordance with the principles and guidelines of good manufacturing practice. However, for the manufacturer to be able to comply with those principles and guidelines, cooperation between the manufacturer and the marketing authorisation holder, when they are different legal entities, is necessary. The obligations of the manufacturer and marketing authorisation holder vis-à-vis each other should be defined in a technical agreement between them." (Ref. Directive 2017/1572, Preamble Point 4).

Thus, it is considered important that there is cooperation and communication between the MAH and manufacturer, when they are different legal entities, and that such arrangements be described in a technical agreement between the parties.

5.3.2. Specific examples of required communications

Example 1 - The use of ionising radiation in the manufacture of medicinal products

An example which illustrates the need for such communication can be found in Annex 12 to the GMP guide. This Annex concerns **the use of ionising radiation** in the manufacture of medicinal products.

It states that the "required dose including justified limits will be stated in the marketing authorisation" (Ref. EU GMP guide Annex 12, Paragraph 3).

This implies a need for communication between the MAH and the manufacturer in relation to the strength and limits of the irradiating dose.

The MAH has a responsibility to ensure that this information is registered in the marketing authorisation, and he is expected to communicate what has been registered with the manufacturer, so that the manufacturer may maintain compliance with the marketing authorisation.

Example 2 - ASMFs and CEPs

Another area of importance in relation to communication processes and responsibilities is where there is an **Active Substance Master File (ASMF)** registered for a marketing authorisation which has both closed and open parts, or where a **Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP)** is registered (or applied for) in the MA. (Note: the information in the CEP replaces those MA dossier sections that normally describe the manufacture and control during manufacture of the active substance (as well as stability data, in cases where the CEP includes a re-test date). Such CEP information will have been evaluated by the European Directorate for the Quality of Medicines (EDQM)).

These approaches are covered by Directive 2001/83/EC:

"For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the (i) detailed description of the manufacturing process, (ii) quality control during manufacture, and (iii) process validation, to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File. In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file" (Ref. Directive 2001/83/EC, Annex 1).

"Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines, shall be presented in the relevant section of this module (i.e. module 3). Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines" (Ref. Directive 2001/83/EC, Annex I).

It is important to note that, irrespective of whether an ASMF or a CEP is in place, *the MAH retains his responsibility for ensuring the quality of the active substance*.

- *The MAH is responsible for ensuring, (via technical agreements), that it, in conjunction with the finished product manufacturer, has access to all relevant information concerning the current manufacture of the active substance;*
- *This requires effective communication processes to be in place between the concerned parties in relation to the manufacture of the active substance;*
- *Such communication processes should also address proposed changes in the manufacturing process or specifications, to enable the MAH to assess the implications of the proposed change on the finished product and to apply for any required variations to the MA, in accordance with the EU Variation Classification Guideline;*
- *In addition, if a CEP is registered in an MA, this does not exempt the MAH from the responsibility to have available a declaration of GMP (signed by the Qualified Person) relating to the GMP*

compliance status of the active substance manufacturer. See the earlier text in this Reflection Paper for information on QP Declarations;

- *The level of knowledge that the MAH has in relation to the manufacture and control of the active substance should be such that it permits the MAH to take responsibility for the quality of the medicinal product. This should not be less than when there is an ASMF registered in the MA.*

In order for the MAH (or applicant) to be able to fulfil the responsibilities referred to above, it is considered that he should ensure that the above requirements are clearly addressed in a technical agreement between the MAH and the active substance manufacturer.

Example 3 – Documentation reflecting what is registered is the MA

A third example is found in Chapter 4 of the GMP guide, in relation to **Documentation**. It states that "Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, as appropriate. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process" (Ref. GMP guide Chapter 4, Paragraph 4.2).

This implies a responsibility for the MAH to ensure that any documents that it provides to the manufacturing sites relating to what is registered in the MA accurately reflect the relevant parts of the MA.

- Examples of such documents might include the release and shelf-life specifications for the product, information in relation to the registered manufacturing process, copies of the registered artwork for the product packaging, etc.;
- It is especially important that documents relating the registered product information intended for the patient or user of the medicine (i.e. labels and leaflets) are in line with the marketing authorisation, and that changes (variations) to these items are communicated to the manufacturing site in a timely manner.

5.3.3. The effectiveness and frequency of communications

It is considered that there should be effective and frequent communications between the MAH and the relevant manufacturing sites*. This is not just in relation to what is registered in the MA, but also, it might concern the results of Product Quality Reviews (PQRs), information about regulatory commitments, proposed changes which may affect modules 1, 2 and 3 of the MA, among other things.*

5.3.4. Documenting communication processes – complexity and legal arrangements

How such communication processes and responsibilities may be documented depends on the relationship between the various entities, and on the complexity of the arrangements that may be in place. Complexity in relation to the supply chain is particularly important to consider when determining what communication processes need to be in place – this can relate to the number and type of different manufacturers in the supply chain, the degree of outsourcing that is in place, the geographic spread of the various actors in the supply chain, etc.

In cases where the MAH and the manufacturer are part of the same overall group of companies, it may be sufficient to document, using SOPs, how the actual communication processes are expected to work. This is as long as those SOPs are approved by both parties and as long as they are referred to within the technical agreement between the parties. In other situations, where the MAH and the manufacturer

are not part of the same overall group of companies, the communication processes and responsibilities should be documented in technical agreements or in contracts, as they may be more complex and at a higher risk of failing.

The two-way flow of information between the parties is important, especially in the context of proposed changes which may require variation applications or regulatory notifications to the competent authority by the MAH. This is also the case with regard to suspected quality defects and potential recall issues which may have been reported to one or other party, but not to both, and which may need to be reported onwards to the competent authority.

5.3.5. Life-cycle considerations

Communication processes and systems should be maintained with care, extending over the product life-cycle (e.g. during the licensing procedure, commercial manufacture, the fulfilment of regulatory commitments, the submission and implementation of post-approval variations, etc.) or at least up until the end of the relationship between the concerned parties. The MAH should ensure that communication systems are in place which will enable it to keep abreast of all developments, changes and commitments relating to the specific product of concern.

5.3.6. Communications with the competent authorities – MA variations

In relation to manufacturing-related MA variations, the MAH has a responsibility via Directive 2001/83/EC to provide the competent authority with information on amendments relative to the information submitted in the dossier. The Directive states that "The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I" (Ref. Directive 2001/83/EC, Article 23 (2)). Similar provisions are referred to in the Veterinary Directive, 2001/82/EC, via Article 27.3.

Some of these articles directly concern GMP-related information, such as Article 8(3) in Directive 2001/83/EC, which relates to, among other things, a description of the manufacturing method and the control methods employed by the manufacturer.

5.3.7. Communications relating to product supply

Robust and timely communications are important in other areas too, not only in ensuring the regulatory compliance status of the product in the marketplace. In relation to ensuring the continued supply of medicinal products for patients and animals, for example, communication processes between MAHs, manufacturers and national competent authorities can play a pivotal role. See Section 5.6 below for further information on this point.

5.3.8. Communications relating to scientific advances

Another area in which effective communication processes can be of significant importance is in the maintenance of MAs in line with scientific advances. Article 23 of Directive 2001/83/EC states that, "after an authorisation has been issued, the authorisation holder must, in respect of the methods of manufacture and control provided for in the application, 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." The Veterinary Directive, 2001/82/EC, has similar wording, via Article 27, in relation to the information provided in Article 12(3)(d) and (i).

The above articles imply a responsibility of the MAH to have communication systems in place with manufacturing sites and other parties which will enable it to keep abreast of scientific and technical progress and advances and to discuss initiatives in this area. This is so that any necessary MA variations can be submitted. This is further discussed in section 5.7 below.

5.3.9. Communicating changes to CTD modules 1, 2 and 3 to the manufacturing sites

As CTD modules 1, 2 and 3 of the MA change over time with the approval of variations and with the introduction of continual improvements, etc., it can be a challenge to retain knowledge at both the MAH and at the manufacturer of what is registered at any one time.

- In this regard, it is considered useful if the copies of these CTD modules as held by the MAH (and by the manufacturer, if applicable) are continually kept updated (by replacing individual documents or Sections within a module with the updated versions) as changes are made to those documents or sections within that module;
- This results in always having up-to-date copies of modules 1, 2 and 3 available as a definitive record of what is registered;
- It can help avoid the need to maintain multiple different documents and document repositories to capture what is registered at any point in time;
- Having such 'live' versions of modules 1, 2 and 3 in place can also facilitate communications between the MAH and the manufacturer in relation to what is registered at any point in time.

5.4. Product Quality Reviews (PQRs)

The area of product quality reviews is a topic that is of a direct relevance to MAHs. This is an area in which the GMP guide is quite prescriptive, in relation to what is expected of the MAH. Chapter 1 of the Guide addresses this topic; and it states the following:

> "The manufacturer and, where different, marketing authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified." (Ref. Chapter 1, Paragraph 1.10).

The GMP guide goes on to state that "Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the product quality review." (Ref. Chapter 1, Paragraph 1.11).

There are several important points in the above text which are useful to consider.

- *The first is a clear obligation on the MAH, when it is not the product manufacturer, to evaluate the results of the PQR and to make an assessment in relation to the need for corrective and preventive actions (CAPAs), and revalidation activities. The text requires both parties to do the above evaluation and assessment work;*
- *The second is the importance that the GMP guide places on this PQR evaluation and assessment work by both parties. This is evident from the requirement in Chapter 1 to apply oversight to those activities, and in two different ways –ongoing management review and self-inspection processes;*

- *Lastly, it is clear from the reference to a technical agreement above that each party has responsibilities in relation to PQR activities. In the case of the MAH, the primary responsibility is to perform the PQR evaluation and assessment work that is referred to above.*

Given the importance that the GMP guide attributes to the involvement of both parties in such work, it is not considered appropriate for the MAH to delegate its evaluation and assessment work to the manufacturer. There are several good and risk-based reasons for this.

- Firstly, there is information to be included and evaluated in PQRs which may be spread across both parties, the MAH and the manufacturer, or primarily held by only one. This includes information concerning complaints (and their investigation), as well as quality-related returns, recalls, MA variations (in terms of their status – submitted, granted or refused), and post-marketing commitments;

- Secondly, there are items to be reviewed in a PQR for which both parties may have had different roles. An example here is the product stability data. The MAH may have outsourced the storage and/or testing of the stability samples to a third party, such as a contract laboratory, which is not the product manufacturer, and the results of the testing may be sent to the MAH, and not directly to the manufacturer by the laboratory. In such a situation, the MAH would have an important role in ensuring that the relevant stability data are included in the PQR and that the data are subject to an adequate review.

The evaluation and assessment of such PQR information by both parties (the MAH and the manufacturer) is important in another way too - it can help mitigate two key risks:

a) The risk of producing PQRs which are incomplete and which are missing important signals, trends and learnings, and

b) The risk of placing batches of a product on the market which are non-compliant with the requirements of the MA.

For example, the MAH may have information which the manufacturer may not necessarily have about the required implementation date of a MA variation concerning the package leaflet, submitted to update the leaflet with certain new safety information about the product.

The MAH's evaluation and assessment work on the PQR is beneficial because it has the potential to verify compliance with the variation implementation requirements, not only via a review of the variations section of the PQR, but also via a review of the change control section. The manufacturer's review gives a related opportunity, to review the status of approved product artwork-related MA variations which were listed in the PQR by the MAH.

In order for an MAH to add value in relation to its PQR activities, it is considered that its role in relation to PQRs should be different from those of the manufacturer. It is recognised that PQRs are documents that are primarily generated by the product manufacturer, not the MAH. Most of the information and data that needs to be included and reviewed in a PQR is firmly in the realm of GMP, and usually resides at manufacturing sites, not at the MAHs. (This includes information relating to change controls, process deviations, rejected batches, critical in-process controls, etc.)

There are several ways in which MAHs may add value in relation to PQRs:

- The MAH can ensure that information that it holds which is relevant to the PQR is actually included in the PQR. This applies, for example, to information relating to product complaints, which the MAH may have received directly from the marketplace and which may not all be known to the manufacturer, as well as information about product recalls, MA variations and post-marketing

commitments. The manufacturer may have some of the above information, but it may not possess all of it, and the MAH can ensure that the contents of the PQR report in these areas are complete;

- The MAH can cross-check the information included in the PQR by the manufacturer against its own records, in order to check whether there are any gaps in the data held by the manufacturer which need to be addressed;
- The MAH can ensure that its evaluation of the results of the PQR is focussed on assessing the MA compliance status of the product during the review period, instead of assessing areas for which the MAH may not have the required competency or expertise such as in relation to analytical method changes, the adequacy of equipment-related corrective actions, and the qualification status of relevant equipment and utilities, e.g. HVAC (heating, ventilation and air conditioning), water, compressed gases, etc.

Overall, an MAH's involvement in PQR activities provides tangible benefits, and further information in this regard is presented in Section 5.7 below, in relation to c*ontinual improvement activities*.

Experience has shown that, when MAHs are not involved in the evaluation and assessment of PQR data and reports, those PQRs appear to be at greater risk of not complying with the requirements of Chapter 1 of the GMP guide, and, more importantly, batches in the marketplace may be at greater risk of having MA non-compliances associated with them.

5.5. Quality defects, complaints and product recalls

Chapter 8 of the GMP guide deals with the above topics. In many companies, the management of complaints, quality defects and recalls is performed centrally within the organisation, and Chapter 8 makes provision for this. It states that "the relative roles and responsibilities of the concerned parties should be documented" and that such central management "should not result in delays in the investigation and management of the issue." (Ref. Chapter 8, Paragraph 8.4).

5.5.1. MAH contact person

It is considered that the MAH should be satisfied with the centralised arrangements that are in place, such as within corporate quality groups. *It is important to also note that the applicant/MAH is expected to have a dedicated responsible person to serve as a contact person for product defects and recalls in the post-authorisation phase – in this regard, the applicant/MAH is expected to provide information on its contact person in the MA-application form* (Ref. MA Application Form in the Notice to Applicants - Volume 2B, Article 6 of Regulation 726/2004 and Annex I to Directive 2001/83/EC, as amended.)

5.5.2. Arrangements for dealing with quality defects and recalls

Chapter 8 places obligations on the MAH, the manufacturer and other parties to define and agree their respective roles and responsibilities with regard to quality defective medicinal products. In this context, the outsourcing of manufacturing and other activities is of relevance here, as outsourcing is often an activity in which the MAH is directly involved.

Chapter 8 also recognises this, stating that "in case of outsourced activities, a contract should describe the role and responsibilities of the manufacturer, the marketing authorisation holder and/or sponsor and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and implementation of risk-reducing actions relating to a defective product." It clarifies that such contracts "should also address how to contact those responsible at each party for the management of quality defect and recall issues. (Ref. Chapter 8, Principle).

5.5.3. Notification of quality defects to competent authorities

There are obligations stated in Chapter 8 which relate to the notification of quality defects to the relevant competent authority, and these are linked with the requirement to notify competent authorities of potential supply restrictions and/or product recall as a consequence of quality defect issues. The MAH often has a direct interest in such notification processes, and it is named in Chapter 8 as a party to such notifications. Chapter 8 states that "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." (Ref. Chapter 8, Paragraph 8.15).

5.5.4. Quality defects with investigational medicinal products

Chapter 8 also addresses situations in which quality defects may occur in investigational medicinal products, and these can also be of relevance to MAHs. The text here states that "In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product should, in cooperation with the sponsor, inform the marketing authorisation holder of any quality defect that could be related to the authorised medicinal product. (Ref. Chapter 8, Paragraph 8.24). This requirement is taken directly from Article 13 of GMP Directive 2003/94/EC, which carries almost identical wording.

5.5.5. Potentially falsified medicines & reporting requirements

The Falsified Medicines Directive (FMD), 2011/62/EU, discussed in detail in Section 6, placed specific reporting obligations on manufacturers in relation to products suspected of being falsified. This is relevant to the topic of quality defects, complaints and recalls, as falsified medicines are considered defective medicines and they can lead to recall actions.

In amending Directive 2001/83/EC with the addition of Article 46 (g), the FMD Directive introduced a responsibility for the manufacturer to inform the competent authority and the MAH immediately of information which indicates that a medicinal product within the scope of its manufacturing authorisation is, or is suspected of being, falsified. (This is required irrespective of whether the medicinal product was distributed within the legal supply chain or by illegal means, including illegal sale via information society services).

The above responsibilities imply that the MAH should have a system in place to receive such quality defect and product falsification reports from manufacturers and it should be able to respond to them in a manner that is appropriate. This is also linked with the requirements of the EU pharmacovigilance legislation, by which the MAH is obliged to have systems in place to deal with adverse reaction reports.

5.5.6. Product recall management

The management of product recalls is a specific area of importance for the MAH to have robust procedures in. This is because the MAH is usually heavily involved in recall decision making with the national competent authorities and in the coordination of recalls, when they are required. Chapter 8 states that the "effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use." It requires such evaluations to "extend to both within office-hour situations as well as out-of-office hour situations" and, when performing such evaluations, it requires consideration to be given "as to whether mock-recall actions should be performed." It also requires such evaluations to be "documented and justified." (Ref. Chapter 8, Paragraph 8.30).

Each of these requirements is applicable to the MAH, given the MAH's role in recall decision making, coordination and management, and it is important that the MAH has systems in place to deal with these activities.

5.5.7. Other notification responsibilities

Directive 2001/83/EC also contains provisions in this area that concern the MAH. Article 123 of the Directive, for example, places an obligation upon the MAH to "notify the Member States concerned forthwith of any action taken by the MAH to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action." (Ref. Directive 2001/83/EC, Article 123).

Note that, in relation to veterinary medicinal products, Directive 2001/82/EC contains a similar (but not identical) provision. It states that "the marketing authorisation holder shall be obliged to notify the Member States forthwith of any action taken by him to suspend the marketing of a veterinary medicinal product or to withdraw a product from the market, together with the reasons for such action if it concerns the effectiveness of the veterinary medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the [European Medicines] Agency." (Ref. Directive 2001/82/EC, Article 91).

Article 123 of Directive 2001/83/EC also requires the MAH to declare if such action is based on any of the grounds set out in Article 116 or Article 117(1). These articles relate to situations in which a view is taken by Member States that "the medicinal product is harmful or that it lacks therapeutic efficacy, or that the risk-benefit balance is not favourable, or that its qualitative and quantitative composition is not as declared." They also relate to situations in which "the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled."

5.6. Maintenance of supply of medicinal products

5.6.1. The MAH's public service obligation

The EU medicines legislation, as well as the GMP guide, place obligations upon the MAH that relate to the supply of its medicinal products and to the maintenance of such supply. For example, Article 81 of Directive 2001/83/EC states the following:

> "The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered."

This directly relates to the avoidance of medicines shortages for patients, and is usually referred to as the *public service obligation*. (Note: There is no equivalent to this in Directive 2001/82/EC, in relation to veterinary medicinal products).

5.6.2. Reporting supply restrictions and problems

In addition, in accordance with Chapter 5 of the GMP guide, the MAH has a responsibility to report restrictions in supply to the relevant competent authorities. In this regard, the MAH may have to rely

upon the manufacturer to notify it of potential supply problems. Chapter 5 states that "The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in 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." (Ref. Chapter 5, Paragraph 5.71)

It is useful to consider what actions may be taken by the MAH in order to minimise the impact on patients as a result of potential supply issues with their medicines.

- *At a starting point, it is considered that the MAH should ensure that the communication arrangements between it and the manufacturer on potential supply issues are agreed and clearly documented in a technical agreement between the parties;*
- *Where the two companies are part of the same overall organisation, the specific details in relation to how the communications processes are intended to work at a practical level may be documented in SOPs, as long as those SOPs are approved by both parties and as long as they are referred to within the technical agreement between the parties;*
- *This can help the MAH fulfil its notification obligations to the relevant competent authorities.*

There is European legislation in place which governs the notification of supply issues to the competent authorities. If the product ceases to be placed on the market of a Member State, either temporarily or permanently, the MAH is required, via Article 23a of Directive 2001/83/EC, to notify the competent authority of that Member State. The Directive requires that such notifications shall, "other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product."

The MAH is also required to inform the competent authority of the reasons for such action in accordance with Article 123(2) of the Directive. This article requires the MAH to notify the Member States concerned forthwith "of any action taken by the MAH to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action."

5.6.3. Possible reasons for supply disruptions – complexity, outsourcing & other factors

There is a variety of factors that may lead to disruptions of supply chains and product shortages for patients and animals. The globalisation of manufacturing and distribution activities is one such factor; it has contributed to the current situation in which many medicinal products are associated with highly complex supply chains, and this level of complexity gives rise to increased risks of problems arising in those supply chains. These can be difficult to resolve in a timely manner, because coupled with this is the added complexity that extensive outsourcing of manufacturing operations brings. Taken together, they can result in long lead times in manufacturing when crisis situations in the supply of medicines occur.

There are many factors which can lead to product supply issues, and these can be quite diverse, ranging from, for example, a lack of robustness in the supply chain of the active substance, to the poor management of MA transfers between companies, resulting in the correct product artwork not being available in a timely manner following such transfers. The movement of manufacturing processes between two sites can also be a factor if it is not planned and managed adequately, especially where there are tight logistics associated with the manufacturing and supply chain activities.

5.6.4. Prevention of product shortages

It is, therefore, important for MAHs to be proactive in their approach to supply chain management, in order to try and prevent product shortages and to meet the public service obligation as set out in Article 81 of Directive 2001/83/EC. In this regard, it is recommended that MAHs carry out proactive and detailed risk assessments of their manufacturing, regulatory and supply chain processes, and to work to address any identified weaknesses in those areas. A number of useful industry guidance documents on preventing (and reacting to) shortages of medicinal products have been published (e.g. by the ISPE and PDA) and these documents provide useful guidance for MAHs in this area.

5.7. Continual improvement activities

Guidance on the need for continual improvement activities was introduced into the GMP guide in 2013, when Chapter 1 was revised to align it with the concepts and terminology described in the ICH Q10 tripartite guideline on the *Pharmaceutical Quality System*.

Chapter 1 states that a Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that "Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge" (Ref. Chapter 1, Paragraph 1.4(xi)). This is relevant to the MAH in several ways, including PQR activities, where the MAH's involvement in PQRs provides tangible benefits.

For example, the responsibility that the MAH has to evaluate the results of PQRs provides it with process and product knowledge which it may not have had before then. This can help the MAH identify, with its manufacturing site partners, the need for specific continual improvement activities to be initiated.

PQR data can also enable the MAH to identify the need for improvement in its own regulatory affairs processes that operate in conjunction with the manufacturing sites. Examples here include the management of MA variations (relating to CTD module 3 / Notice to Applicants Part 2) of the MA dossier, the support that the MAH provides manufacturing sites in relation to site change control activities (via the provision of regulatory impact assessments for specific change control proposals), amongst others.

5.7.1. Scientific advances

The concept of continual improvement in medicines manufacturing is related to advances in science. Articles 23 and 27 of Directives 2001/83/EC and Directive 2001/82/EC, respectively, require MAHs to maintain MAs in line with scientific advances. Article 23 states that, after an authorisation has been issued, "the authorisation holder must, in respect of the methods of manufacture and control" provided for in the marketing authorisation application, 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 27 of the Veterinary Directive has similar wording.

- *The above requirements place a responsibility on the MAH to work with the manufacturing sites on an ongoing basis in order to incorporate generally accepted scientific methods into the registered methods of manufacture and the registered controls;*
- *The MAH also has the responsibility to ensure that any variation applications which may be required in light of the above changes, are submitted to keep the marketing authorisation up-to-date;*

- *This means that, for the manufacturing process, the process description as included in CTD module 3 / Notice to Applicants Part 2 should be updated, where necessary, to include sufficient details according to current guidelines. In some cases, consideration should also be given to updating the manufacturing process itself.*

It is considered also that, with regard to Article 23 of Directive 2001/83/EC, a company's internal manufacturing documents which describe the manufacturing process should be kept updated in light of scientific and technical progress and that they contain sufficiently detailed information so as to ensure that key manufacturing details are not lost when site transfers occur.

Regarding updates to the methods of control, the MAH is required to ensure that material and product specifications registered in the MA include tests according to the current pharmacopoeia and quality guidelines, and analytical methods should be able to detect/quantify relevant impurities to ICH and VICH thresholds.

In cases where a Ph. Eur. monograph is revised in line with scientific advances to control an active substance, it can be useful for an MAH to work with the manufacturing sites and consider the need for early testing of the substance in question according to the draft revised monograph, and to submit comments on the draft monograph to the EDQM, if necessary. Such activities involving the MAH and manufacturer could be described in a technical agreement.

5.7.2. Other references to continual improvement

There are other references to continual improvement in the GMP guide also which have relevance for the MAH. For example, Chapter 7, on Outsourcing, states that "the Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement" (Ref. Chapter 7, Paragraph 7.7). *This places a responsibility upon the MAH to perform such review and monitoring activities in cases when it is a contact giver for an outsourced operation involving medicines manufacturing. It is considered that part of this responsibility may be fulfilled through an MAH's evaluation and assessment of the results of PQRs, as PQR data can be indicative of the performance of a manufacturer in the manufacture of a product.*

5.7.3. Updating manufacturing processes in line with changes to the EU GMP guide

Finally, it is important to note that the MAH has some responsibility in ensuring that updates to the GMP guide are incorporated at manufacturing site level. This is because, in Directive 2001/83/EC, Annex I, it is stated that "the manufacturing process shall comply with the requirements of Directive 91/356/EEC [since replaced in 2003 by Directive 2003/94/EC] laying down the principles and guidelines of GMP for medicinal products for human use and with the principles and guidelines on GMP, published by the Commission in the rules governing medicinal products in the EC, Volume 4." (It is noted that the Veterinary Directive, 2001/82/EC, has similar wording in the Introduction and General Principles section, in Paragraph 4).

The above relates to the manufacturing process as described in the MA, and as it is the MAH who seeks to register the manufacturing process in the dossier, the above Annex I requirement places an obligation upon the MAH to ensure that the registered manufacturing process is in line with current GMP guidance. This is relevant in the context of continual improvement, because the GMP guide undergoes periodic improvement activities itself.

6. Falsified Medicines Directive (FMD)-related responsibilities

The MAH has a number of responsibilities related to the Falsified Medicines Directive (FMD) 2011/62/EU and the related Delegated Regulations (including the Safety Features Regulation 2016/161). One of those responsibilities, as discussed in Section 5.2 of this Reflection Paper (Audits & Qualification Activities), relates to the need to confirm the GMP status of the active substance manufacturer by means of GMP audits. This responsibility is stated in Article 8(ha) of Directive 2001/83/EC, which originated in the FMD Directive.

6.1.1. Safety features

Other FMD-related responsibilities concern safety features on product packaging.

- Commission Delegated Regulation (EU) 2016/161 sets out what is expected of the MAH in relation to the upload to the repositories system of pack serialisation data, as well as responsibilities in relation to the decommissioning of pack serialisation codes;
- Article 33 of this Regulation requires the MAH to ensure that the information of unique identifier and various additional defined data about the medicinal product and its distribution are "uploaded to the repositories system before the medicinal product is released for sale or distribution by the manufacturer, and that it is kept up to date thereafter." (Note that the Q&A Document on the Commission's Website provides additional guidance in this area – see Q&A 4.5).

It is considered that the QP who certifies batches prior to their release to the market should be satisfied with the arrangements that have been put in place by the MAH for the upload of the safety features data to the repositories system. (In relation to QP responsibilities in this general area, it is useful to note that Annex 16 to the GMP guide places a responsibility on the QP to ensure that the following point is secured, that:

> "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." (Ref. Annex 16, Paragraph 1.7.21).
>
> Annex 16 indicates that this task may be delegated to "appropriately trained personnel or third parties", and in this regard, the Annex recognises that the QP will "need to rely on the pharmaceutical quality system" that is in place and it requires the QP to have "on-going assurance that this reliance is well founded". (Ref. Annex 16, Paragraph 1.7).

It is considered that the transfer of the unique identifier (UI) data from the location where they were generated until their upload into the EU hub is performed in a secure manner and in such as a way that the integrity of data is not compromised.

6.1.2. The repositories system & MAH responsibilities

The repositories system is expected to be established and managed by the MAHs (Ref. Paragraph 28 of the preamble text of Delegated Regulation (EU) 2016/161). Article 32 of the Delegated Regulation sets out the required structure of the repositories system – there should be a central information and data router (known as the European Hub) and repositories which serve the territory of one or multiple Member States. Those repositories are required to be connected to the EU-Hub. The European Medicines Verification Organisation (EMVO) is the organisation representing stakeholders who have taken responsibility for the formation of the European Medicines Verification System (EMVS/EU-Hub).

Each European country is expected to implement a National Medicines Verification System (NMVS) which will be set up and managed by a National Medicines Verification Organisation (NMVO). The MAHs are expected to liaise with both the EMVO and the relevant NMVOs for the concerned products.

Various items of information are required to be uploaded to the repositories system, including:

- The data elements of the unique identifier;
- The coding scheme of the product code;
- The name and the common name of the medicinal product, the pharmaceutical form, the strength, the pack type and the pack size;
- The Member State or Member States where the medicinal product is intended to be placed on the market;
- The name and address of the manufacturer placing the safety features;
- A list of wholesalers who are designated by the MAH, by means of a written contract, to store and distribute the products covered by the marketing authorisation on his behalf.

This and other information is intended to be stored in all of the national or supranational repositories serving the territory of the Member State, or Member States, where the medicinal product bearing the UI is intended to be placed on the market for at least one year after the expiry date of the medicinal product, or five years after the product has been released for sale or distribution, whichever is longer. The same responsibility applies to persons responsible for placing parallel imported or parallel distributed medicinal products onto the market.

6.1.3. Serialisation data - uploading responsibilities

The MAH may delegate the uploading of the information laid down in Article 33(2) to a third party; such delegation is expected to be documented in a written agreement between both parties. It is important to note that the MAH may subcontract, or delegate, data uploading only to parties which perform the data upload by means of infrastructure, hardware and software, which is physically located within the EEA. Importantly, the MAH remains legally responsible for such tasks, as stated in the document titled 'Safety Features For Medicinal Products For Human Use; Questions And Answers', available on the European Commission's website.

In relation to Contract Manufacturing Organisations (CMOs), these will not be permitted to on-board to the EU-Hub, and it is considered that the relevant MAH needs to ensure that appropriate arrangements are put in place in this regard, in order to ensure the secure upload of the serialisation data.

6.1.4. Unique identifier decommissioning responsibilities

In relation to decommissioning, which is a term that relates to various pack statuses within the repositories, including the pack status called 'supplied', it is an MAH responsibility according to Article 40 of the Delegated Regulation to ensure the decommissioning of pack codes in the case of a product recall or withdrawal. Article 40 states that "the marketing authorisation holder shall promptly take all the following measures:

> (a) ensure the decommissioning of the unique identifier of a medicinal product which is to be recalled or withdrawn, in every national or supranational repository serving the territory of the Member State or Member States in which the recall or the withdrawal is to take place;

(b) ensure the decommissioning of the unique identifier, where known, of a medicinal product which has been stolen, in every national or supranational repository in which information on that product is stored;

(c) indicate in the repositories referred to in points (a) and (b) that that product has been recalled or withdrawn or stolen, where applicable."

The same responsibility applies to persons responsible for placing parallel imported or parallel distributed medicinal products onto the market.

It is worth noting that "decommissioned" as such is not a status in the system; multiple statuses that are different from "active" have been developed in the EMVS by EMVO, such as "RECALLED", "DESTROYED" or "STOLEN". All of these are considered as "decommissioned".

For the above responsibilities to be met by the MAH, it is considered that there should be robust communication systems in place between the MAH and the manufacturer (or other third party) to whom such tasks have been delegated. This is because the various data elements that must be *uploaded to the repositories system may be held by the different entities – the manufacturer will likely hold the actual pack serialisation codes per batch, while the MAH may hold the information about the wholesalers which have been designated by it to store and distribute the product, as well as information about the distribution of free medical samples and about product recall actions.*

For the above responsibilities to be met by the MAH, it is considered that there should be robust communication systems in place between the MAH and the manufacturer (or other third party) to whom such tasks have been delegated. This is because the various data elements that must be uploaded to the repositories system may be held by the different entities – the manufacturer will likely hold the actual pack serialisation codes per batch, while the MAH may hold the information about the wholesalers which have been designated by it to store and distribute the product, as well as information about the distribution of free medical samples and about product recall actions.

7. Conclusion

The EU guide to GMP refers in several places to MAH companies and their responsibilities in relation to GMP. Such responsibilities are spread over various chapters and annexes of the guide, and are quite numerous. There are also various GMP-related responsibilities for MAHs stated in applicable medicines legislation. There appears, however, to be a lack of clarity and understanding as to what these responsibilities actually are in their totality, and what they mean for MAHs, especially at a practical level. Thus, it was considered that it would be of benefit to MAHs (and also to manufacturers, GMP Inspectors and other stakeholders) if these responsibilities were documented in one place and adequately explained. This Reflection Paper seeks to address this.

While it is recognised that many MAH companies are not directly engaged in the manufacture of medicinal products themselves, GMP is an area that has direct relevance for them. Indeed, it is of interest that the GMP guide states the following: "…the ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorisation holder". A significant part of the performance of a medicinal product relates to compliance with the GMP requirements during product manufacturing.

This Reflection Paper sets out what the various responsibilities for MAHs are and it seeks to explain their practical implications. It essentially seeks to present a more complete picture of the regulatory environment with respect to GMP in which the MAH operates. It groups the responsibilities under a number of different *themes*; this is in an effort to illustrate the general areas in which the responsibilities lie, and to provide a holistic view of them. It is intended that this Reflection Paper will

provide increased clarity for MAHs in this area, and that it will serve as a useful resource for MAHs when designing (or reviewing) their internal systems as well as their interactions with manufacturing sites.

Overall, this Reflection Paper is intended to be of assistance to MAHs as they work with the product manufacturers and other stakeholders to facilitate compliance of the medicines placed on the market, in terms of GMP and the MA. This ultimately serves the interests of patients and animals, as it contributes to ensuring the availability of high quality, safe and effective medicines.

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(Note: All websites were accessed in April 2019)