



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 September 2016
EMA/582064/2016
GMP/GDP Inspectors Working Group

Concept paper on Good Manufacturing Practice and Marketing Authorisation Holders

Agreed by GMP/GDP Inspectors Working Group	May 2016
Start of public consultation	October 2016
End of consultation (deadline for comments)	End December 2016

Comments should be sent to adm-gmdp@ema.europa.eu

Keywords	Good practice, marketing authorisation holder, MAH
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1. Introduction

The current EU Guide to GMP refers in several places to Marketing Authorisation Holder (MAH) companies and their responsibilities in relation to GMP ensuring that the manufacturing authorisation holder can comply with GMP. These range from a responsibility to perform a task (e.g. review of periodic quality review), to acting at the interface with manufacture and control of the medicinal product (e.g. provision of current dossier information to facilitate the manufacturer's compliance with the marketing authorisation). These responsibilities for MAHs are spread over various chapters and annexes of the Guide, and are quite numerous. 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 at a practical level.

It is considered that these existing requirements could be documented in a better way, so that MAHs (and manufacturers) have increased clarity as to what their respective responsibilities are. It is not intended that this work should introduce any new responsibilities on MAHs. This concept paper presents a proposal for how this might be achieved.

2. Problem statement

It is considered that there is a lack of clarity and awareness among MAHs as to the various responsibilities that relate to them, as stated in the current EC Guide to GMP and in related legislation, enabling compliance of the manufacturing authorisation holder with GMP. This in turn has led to a situation in which there is a lack of knowledge and understanding among some MAH companies at least on the need to comply with those responsibilities. This is based on the experiences of those inspectorates that perform regulatory compliance inspections at the offices of MAH companies, as well on the general experiences of GMP Inspectors.

The following are just some of the responsibilities that relate to MAHs as stated in the current EC Guide to GMP:

- Chapter 1 of the Guide, in Section 1.11 on PQRs, places a clear responsibility on MAHs, in cases where they are not the manufacturer, to evaluate the results of the PQR review and to make an assessment as to whether corrective and preventive action or any revalidation should be undertaken. In many cases, experience has shown that MAHs are often not performing such PQR evaluations.
- In Chapter 7, Outsourcing, paragraph 7.3 states that, where the marketing authorization holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.
- In Chapter 8, the role and responsibilities of the MAH (and other parties) in relation to the assessment, decision-making, and dissemination of information concerning quality defects, risk-reducing actions and notification of possible disruption in supply are referred to.
- Annex 2, in paragraph 36, indicates that MAHs have tasks in relation to human tissues and cells that are used as starting materials for biological medicinal products. It states that a technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue

establishments, sponsors, MA Holder) which defines the tasks of each party, including the Responsible Person and Qualified Person.

- Annex 12 sets out obligations for MAHs in relation to irradiation cycles – these relate to approving the design of the irradiation cycles, and agreeing the location for retention of irradiation cycle records.
- Annex 16, paragraph 4.2, sets out a requirement for MAHs to be able to identify the site and QP responsible for certifying each batch (in the case of multiple sites authorised to manufacture / import / certify the same product).
- In Annex 19, there are MAH responsibilities set out in paragraphs 6.1 and 10.2 for ensuring that reference and retention samples are taken, and stored.

Perhaps the strongest reference in the EC Guide to GMP in relation to the responsibilities of MAHs is in Annex 16. This states that 'the ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorisation holder (MAH).

In relation to legislation, there are also specific obligations imposed on MAHs that relate to GMP and product quality considerations generally. For example:

- Article 23 of Directive 2001/83/EC and Article 27 Directive 2001/82/EC requires marketing authorisation holders to maintain Marketing Authorisations (MAs) in line with scientific advances, and this has direct relevance for manufacturing sites. The article 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 MA 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.

There are also provisions in the legislation related to product supply obligations of MAHs.

- Article 81 of Directive 2001/83/EC concerns the supply of medicinal products, and it requires MAHs to, within the limits of their responsibilities, ensure continued and appropriate supplies so that the needs of patients are covered. (In relation to this, Chapter 5 of the EC Guide to GMP, paragraph 5.71, requires manufacturers to report to the MAHs in a timely manner any constraints in manufacturing operations which may result in abnormal restriction in the supply, to facilitate reporting of the restriction in supply by the MAH to the relevant competent authorities).

Taking all of the above into account, and considering the disparate places within the GMP Guide (and within the legislation) that cite various responsibilities of MAHs to enable the manufacturers' compliance with GMP, it is considered that efforts should be made to bring clarity to this area.

It would be of benefit to MAHs (and indeed manufacturers, GMP Inspectors and other stakeholders) if these responsibilities were documented in one place and adequately explained.

3. Discussion (on the problem statement)

The issues outlined above are not without important consequences. The way in which MAHs are expected to interact with the manufacturing sites registered in a marketing authorisation is not

sufficiently clear, given the diverse ways in which the various MAH responsibilities are set out in the EC Guide to GMP, and differing (often complex) supply chains.

Also, some MAHs are not clear on their responsibilities. When MAHs and manufacturers are different companies and/or separate legal entities, it becomes increasingly important to clearly define the role of the MAH in facilitating GMP compliance at outsourced manufacturing and control organisations.

Furthermore, certain important activities of MAHs with respect to ensuring GMP and MA compliance are not well addressed in the current EC Guide to GMP. For example, providing the various manufacturing sites with the necessary information contained within CTD Modules 1 and 3 from the MA in order to enable the sites to manufacture medicines in compliance with the MA.

Furthermore, the management of MA variations and regulatory commitments (made between a MAH and a competent authority), and the communication of those to the various manufacturing sites, can have a significant impact on MA compliance if not done correctly. The importance of robust communication processes in this area will likely assume increased importance as we move towards greater flexibility in post-approval lifecycle change management (e.g. more “do and tell” variations).

4. Recommendation

It is recommended that the GMP/GDP Inspectors Working Group (GMP/GDP IWG) should produce a reflection paper intended for Part III of the EU GMP Guide or in another appropriate location (e.g. as proposed by the GMP/GDP IWG). This would capture all of the responsibilities that apply to MAH companies to enable manufacturers to comply with GMP. It would also result in a more complete picture of the regulatory environment with respect to GMP in which the MAH operates.

As part of this, the Working Group should also provide any clarifications or explanations in the reflection paper on those responsibilities, where required.

A reflection paper should also provide a degree of flexibility in relation to the management of future GMP Guide changes - by structuring the paper in a way that highlights the general themes of the MAH’s responsibilities.

5. Proposed timetable – for discussion at IWG

- Release of concept paper for public consultation: October 2016
- Deadline for comments on concept paper: end of December 2016
- Preparation of a reflection paper by the drafting group: March 2017
- Review of the reflection paper at the GMP/GDP Inspectors Working Group: May 2017
- Agreement of the reflection paper: June 2017

6. Resource requirements for preparation

A drafting group consisting of a small number of inspectors from participating member states will be required to evaluate comments arising from the public consultation of this concept paper and to prepare the Reflection Paper.

7. Impact assessment (anticipated)

It is anticipated that this work will have a positive impact on the regulatory compliance status of medicines produced in the EEA (and consequently on public and animal health). This is because clearer and more informed guidance on the GMP-related responsibilities that apply to MAH companies will be available.

This work should enable MAHs to understand and to fulfil their responsibilities in relation to GMP more effectively and comprehensively.

It is anticipated that this work will also have a positive impact for manufacturers of medicinal products and active substances. As these companies work to produce medicines that are in compliance with the requirements of the marketing authorisation, their own relative responsibilities in relation to regulatory compliance will be more clearly defined.

8. Interested parties

This work should be of interest to Marketing Authorisation Holders as well as manufacturers of medicinal products and active substances.

9. References to literature, guidelines, etc.

- The EC Guide to GMP
- Directives 2001/83/EC, 2001/82/EC, 2003/94/EC, 91/412/EEC
- The Compilation of Union Procedures on Inspections and Exchange of Information