



**EUROPEAN COMMISSION**  
HEALTH AND CONSUMERS DIRECTORATE-GENERAL  
Health systems and products  
**Medicinal products – quality, safety and efficacy**

Brussels,  
SANCO/D/6/SF/mg/ddg1.d.6(2013)17926  
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**GUIDELINES ON THE FORMALISED RISK ASSESSMENT FOR ASCERTAINING THE  
APPROPRIATE GOOD MANUFACTURING PRACTICE FOR EXCIPIENTS OF MEDICINAL  
PRODUCTS FOR HUMAN USE**

**DRAFT SUBMITTED FOR PUBLIC CONSULTATION**

Stakeholders are invited to comment on this draft by 30 April 2013 at the latest. Responses should be sent preferably by e-mail to [sanco-pharmaceuticals-d6@ec.europa.eu](mailto:sanco-pharmaceuticals-d6@ec.europa.eu), or by post to Unit SANCO/D/6, DM24 02/050, BE-1049 Brussels.

When sending your comments and responses, you should state whether you are a stakeholder association or a private individual. If you represent an association, please indicate clearly what type of association this is (excipient manufacturer, medicinal products manufacturer, importer etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

All comments and responses will be made publicly available on the 'Europa website' on pharmaceuticals once the consultation period is over. If you do not wish your contribution to be made public please indicate this clearly and specifically in the documentation you send us (i.e. not just in the covering letter or e-mail). In this case, only an indication of the contributor will be disclosed.

Professional organisations are invited to register in the Union's Register for Interest Representatives (<http://europa.eu/transparency-register/>) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structures of interest representatives.

## 1. INTRODUCTION

1. Directive 2011/83/EC provides, in Article 46(f), as follows:

*“The holder of the manufacturing authorisation shall ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is. This shall be ascertained on the basis of a formalised risk assessment in accordance with the applicable guidelines referred to in the fifth paragraph of Article 47. Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects. The holder of the manufacturing authorisation shall ensure that the appropriate good manufacturing practice so ascertained, is applied. The holder of the manufacturing authorisation shall document the measures taken under this paragraph”*

2. The fifth paragraph of Article 47 of Directive 2001/83/EC provides that :

*“The Commission shall adopt guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients referred to in the second paragraph of point (f) of Article 46.”*

3. These guidelines are presented below:

- Section 2: “Determination of appropriate GMP based on type of excipient” provides guidance on how to assess and rank the risk presented by the excipient.
- Section 3: “Determination of Excipient Manufacturer’s Risk Profile” covers identification of appropriate GMP and assessment, ranking and control of the risk profile of the excipient manufacturer.
- Section 4: “Confirmation of Application of Appropriate GMP” presents guidance on how to manage the risks of use of the excipient on an on-going basis.

4. The excipient risk assessment/risk management procedure should be incorporated in the Quality Management System of the Manufacturing Authorisation Holder.
5. Importers of medicinal products must have the risk assessment/management documentation for appropriate GMP for excipients available on site.

## 2. DETERMINATION OF APPROPRIATE GMP BASED ON TYPE OF EXCIPIENT

6. The Quality Risk Management guidelines (ICHQ9) in Part III of Eudralex, the Rules Governing Medicinal Products in the European Union, Volume 4 (*EU Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use* – hereafter 'EU-GMP') provide principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include excipients.
7. These Quality Risk Management principles should be used to assess the risks presented to the quality, safety and function of each excipient and to classify the

excipient in question as “low risk”, “medium risk” or “high risk”. Quality risk management tools such as those listed in ICH Q9 (for example, hazard analysis and critical control points – HACCP, etc.) should be used for this purpose.

8. For each excipient used, the Manufacturing Authorisation Holder should identify the risks presented to the quality, safety and function of each excipient from its source (be that animal, mineral, vegetable, synthetic etc.) through to its incorporation in the finished pharmaceutical dose form. Areas for consideration would include:
  - Transmissible Spongiform Encephalopathy
  - Potential for viral contamination
  - Potential for microbiological or endotoxin/pyrogen contamination
  - Potential, in general, for any impurity originating from the raw materials (e.g. aflatoxins, pesticides) or generated as part of the process and carried over (e.g. residual solvents and catalysts)
  - Sterility assurance (for excipients claimed to be sterile)
  - Use of dedicated equipment and/or facilities
  - Environmental control and storage conditions
9. Additionally, with respect to the use and function of each excipient the Manufacturing Authorisation Holder should also consider:
  - The pharmaceutical form and use of the medicinal product containing the excipient (e.g. ointment product, injection/infusion etc.)
  - The function of the excipient in the formulation (e.g. lubricant in a tablet product or preservative material in a liquid formulation etc.)
  - The quantity used of the excipient for the manufacture of medicinal products
  - Daily patient intake of the excipient
  - Any known quality defects both globally and at a local company level related to the excipient
  - Whether the excipient is a composite
  - Potential impact on the Critical Quality Attributes of the medicinal product
10. Having established and documented the risk profile of the excipient, the Manufacturing Authorisation Holder should establish and document the elements of EU-GMP that he believes are needed to be in place in order to control and maintain the quality of the excipient (e.g. EU-GMP, Part I, Annex 1 and Annex 2, Part II etc.).
11. This will vary depending on the source, the supply chain and the subsequent use of the excipient, but as a minimum the following high level GMP principles should be considered:
  - a) Establishment and implementation of an effective Quality Assurance system
  - b) Sufficient competent and appropriately qualified personnel
  - c) Defined job descriptions for managerial and supervisory staff responsible for manufacturing and quality activities

- d) Training programmes for all staff involved in manufacturing and quality activities
- e) Training programmes related to health, hygiene and clothing
- f) Provision and maintenance of premises and equipment appropriate to the intended operations
- g) Documentation system(s) covering all processes and specifications for the various manufacturing and quality operations including retention of batch documentation, which should be for at least one year after the expiry date of the excipient batch to which it relates
- h) Systems for coding and identifying starting materials, intermediates and excipients to allow full traceability
- i) Provision and maintenance of an independent quality control department under the authority of the person nominated as responsible for overall Quality Control
- j) Retention of records for starting materials and excipients and retention of samples of excipients for the periods required by EU GMP
- k) Systems to ensure that any activity contracted out is subject to a written contract
- l) Maintenance of an effective system whereby complaints are reviewed and products may be recalled
- m) Regular self-inspection programmes
- n) Any other (non-GMP) measures required to manage or control the identified risk.

### **3. DETERMINATION OF EXCIPIENT MANUFACTURER'S RISK PROFILE**

- 12. A gap analysis of the required GMP against the activities and capabilities of the excipient manufacturer should then be performed.
- 13. Data/evidence to support this should be obtained through audit or from information received from the excipient manufacturer.
- 14. Quality system certification or accreditation held by the excipient manufacturer and the standards against which this has been granted should be considered as this may meet the required Good Manufacturing Practices.
- 15. Any gaps identified between the required GMP and the activities and capabilities of the excipient manufacturer should be documented. Furthermore, the Manufacturing Authorisation Holder should perform a further risk assessment to determine the risk profile (i.e. low risk, medium risk or high risk, for that excipient manufacturer). It is recommended that the Quality Risk Management guidelines (ICHQ9) in Part III of Eudralex, the Rules Governing Medicinal Products in the European Union, Volume 4 are used to classify the risk profile of the excipient manufacturer. Quality risk management tools such as those listed in there (HACCP etc.) should be used for this.

16. The Manufacturing Authorisation Holder should have a series of risk mitigation strategies ranging from acceptance through control to unacceptable for the different risk profiles and based on these a control strategy (e.g. audit, document retrieval and testing) should be established.

#### **4 Confirmation of application of appropriate GMP**

17. Once the “appropriate GMP” for the excipient and the risk profile of the manufacturer has been defined on-going risk review should be performed through mechanisms such as:
  - a) Number of defects on received batches of excipients
  - b) Type/severity of defects on excipients
  - c) Loss of relevant quality system accreditation by excipient manufacturer
  - d) Observation of trends in drug product quality attributes (this will depend on the nature and role of excipient)
  - e) Audit (re-audit) of excipient manufacturer.