Guidelines

of 19 March 2015

on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use

(Text with EEA relevance)

(2015/C 95/02)

Introduction

These guidelines are based on the fifth paragraph of Article 47 of Directive 2001/83/EC ([1]).

According to the second paragraph of Article 46(f) of Directive 2001/83/EC, the manufacturing authorisation holder is required to ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice (GMP) is. The appropriate GMP for excipients of medicinal products for human use shall be ascertained on the basis of a formalised risk assessment in accordance with these guidelines. The 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 manufacturing authorisation holder shall ensure that the appropriate GMP ascertained is applied. The manufacturing authorisation holder shall document the measures taken.

The excipient risk assessment/risk management procedure should be incorporated in the pharmaceutical quality system of the manufacturing authorisation holder.

Manufacturing authorisation holders should have the risk assessment/management documentation for appropriate GMP for excipients available on site for review by GMP inspectors. Consideration should be given to sharing relevant information from the risk assessment with the excipient manufacturer to facilitate continuous improvement.

A risk assessment as set out in these guidelines should be carried out for excipients for authorised medicinal products for human use by 21 March 2016.

CHAPTER 1 — SCOPE

1.1. These guidelines apply to the risk assessment for ascertaining the appropriate GMP for excipients for medicinal products for human use. According to Article 1(3b) of Directive 2001/83/EC, an excipient is any constituent of a medicinal product other than the active substance and the packaging material.

1.2. These guidelines do not cover substances added to stabilise active substances that cannot exist on their own.

CHAPTER 2 — DETERMINATION OF APPROPRIATE GMP BASED ON TYPE AND USE OF EXCIPIENT

2.1. In EudraLex Volume 4, Guidelines for Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part III: GMP related documents, ICH guideline Q9 on Quality Risk Management (ICH Q9), principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality, including excipients, can be found.

2.2. 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, e.g. as low risk, medium risk or high risk. Quality risk management tools such as those listed in EudraLex Volume 4, Part III, ICH Q9 (e.g. hazard analysis and critical control points — HACCP) should be used for this purpose.

2.3. For each excipient from each manufacturer 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 should include, but are not limited to:

(i) transmissible spongiform encephalopathy;

(ii) potential for viral contamination;

([1]) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

(iii) potential for microbiological or endotoxin/pyrogen contamination;

(iv) potential, in general, for any impurity originating from the raw materials, e.g. aflatoxins or pesticides, or generated as part of the process and carried over, e.g. residual solvents and catalysts;

(v) sterility assurance for excipients claimed to be sterile;

(vi) potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities;

(vii) environmental control and storage/transportation conditions including cold chain management, if appropriate;

(viii) supply chain complexity;

(ix) stability of excipient;

(x) packaging integrity evidence.

2.4. Additionally, with respect to the use and function of each excipient, the manufacturing authorisation holder should consider:

(i) the pharmaceutical form and use of the medicinal product containing the excipient;

(ii) the function of the excipient in the formulation, e.g. lubricant in a tablet product or preservative material in a liquid formulation, etc.;

(iii) the proportion of the excipient in the medicinal product composition;

(iv) daily patient intake of the excipient;

(v) any known quality defects/fraudulent adulterations, both globally and at a local company level related to the excipient;

(vi) whether the excipient is a composite;

(vii) known or potential impact on the critical quality attributes of the medicinal product;

(viii) other factors as identified or known to be relevant to assuring patient safety.

2.5. Having established and documented the risk profile of the excipient, the manufacturing authorisation holder should establish and document the elements of EudraLex Volume 4 that he believes are needed to be in place in order to control and maintain the quality of the excipient, e.g. Annex 1 or/and Annex 2; Part II: Basic Requirements for Active Substances used as Starting Materials.

2.6. These elements 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 elements should be considered by the manufacturing authorisation holder:

(i) establishment and implementation of an effective pharmaceutical quality system;

(ii) sufficient competent and appropriately qualified personnel;

(iii) defined job descriptions for managerial and supervisory staff responsible for manufacturing and quality activities;

(iv) training programmes for all staff involved in manufacturing and quality activities;

(v) training programmes related to health, hygiene and clothing as identified as necessary to the intended operations;

(vi) provision and maintenance of premises and equipment appropriate to the intended operations;

(vii) documentation system(s) covering all processes and specifications for the various manufacturing and quality operations;

(viii) systems for coding and identifying starting materials, intermediates and excipients to allow full traceability;

(ix) qualification program of suppliers;

(x) system for quality control of the excipient and a responsible person independent from production to release the batches;

(xi) retention of records for incoming materials and excipients and retention of samples of excipients for the periods required by EudraLex Volume 4, Part II;

(xii) systems to ensure that any activity contracted out is subject to a written contract;

(xiii) maintenance of an effective system whereby complaints are reviewed and excipients may be recalled;

(xiv) change management and deviation management system;

(xv) self-inspection program;

(xvi) environmental control and storage conditions.

CHAPTER 3 — DETERMINATION OF EXCIPIENT MANUFACTURER'S RISK PROFILE

3.1. After determination of the appropriate GMP, a gap analysis of the required GMP against the activities and capabilities of the excipient manufacturer should be performed.

3.2. Data/evidence to support the gap analysis should be obtained through audit or from information received from the excipient manufacturer.

3.3. Certification of quality systems and/or GMP held by the excipient manufacturer and the standards against which these have been granted should be considered as such certification may fulfil the requirements.

3.4. 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, e.g. low risk, medium risk or high risk, for that excipient manufacturer. EudraLex Volume 4, Part III, ICH Q9 should be used for that purpose. Quality risk management tools such as those listed there — HACCP etc. — should be used for this.

3.5. The manufacturing authorisation holder should have a series of 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.

CHAPTER 4 — CONFIRMATION OF APPLICATION OF APPROPRIATE GMP

4.1. Once the appropriate GMP for the excipient and the risk profile of the excipient manufacturer have been defined, ongoing risk review should be performed through mechanisms such as:

(i) number of defects connected to batches of excipient received;

(ii) type/severity of such defects;

(iii) monitoring and trend analysis of excipient quality;

(iv) loss of relevant quality system and/or GMP certification by excipient manufacturer;

(v) observation of trends in drug product quality attributes; this will depend on the nature and role of excipient;

(vi) observed organisational, procedural or technical/process changes at the excipient manufacturer;

(vii) audit/re-audit of excipient manufacturer;

(viii) questionnaires.

Based on the outcome of the risk review, the established control strategy should be reviewed and revised if needed.