New EU Commission Guidelines

GMP for excipients of medicinal products for human use

The EU Commission adopted on 19 March 2015 its guidelines aiming at helping Manufacturing Authorisation Holders (MAH) of medicinal products to perform a formalised risk assessment for ascertaining the appropriate GMP for excipients they are using.

MAH shall ensure that the determined appropriate GMP are applied by the excipients manufacturers.

Flavourings used in medicinal products are considered as excipients.

Publication and background

The EU Commission published Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use. [OJ C 95/10, 21.3.2015]
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2015.095.01.0010.01.ENG

These guidelines were adopted in application of Article 47 of Directive 2001/83 regarding medicinal products for human use. New requirements on GMP for excipients were introduced with Directive 2011/62 modifying Directive 2001/83, especially Article 46 (f):

- The manufacturing authorisation holder (MAH), i.e. the manufacturer of medicinal products, is required to ensure that the excipients are suitable for use in medicinal products;
- To this end, the MAH shall determine the appropriate GMP for excipients on the basis of a formalised risk assessment and ensure that it is applied.

Date of application: A risk assessment as set out in these guidelines should be carried out for excipients **by 21 March 2016.**

Definition of excipient: Any constituent of a medicinal product other than the active substance and the packaging material.

- **Flavourings used in medicinal products are considered as excipients.**

Attention should be paid to the fact that the provisions of Article 46 (f), and thus also the COM Guidelines, apply first to MAH who are responsible for the determination of GMP and the control of their application.
Obviously the COM Guidelines are also highly relevant for excipient manufacturers as they are required to apply GMP determined by MAH.

Principles and steps of the risk assessment

The guidelines describe three main steps of the risk assessment mechanism:

Step 1. Determination of appropriate GMP by the manufacturing authorisation holder (Chapter 1)

COM recommends the use of guidance already existing regarding GMP for medicinal products: EudraLex Volume 4, part III "GMP related documents", ICH guideline Q9 on Quality Risk Management.

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Objectives:

- To assess the risks presented to the quality, safety and function of excipient.
- To classify the excipient, e.g. as low, medium or high risk.

It should be noted that ICH Guideline Q9 gives examples of recognized risk management tools. One of these tools is HACCP which is especially relevant for flavourings manufacturers[1].

Non-comprehensive lists of hazards and quality parameters that should be considered from the excipient source to its use and function are provided (2.3 & 2.4), together with a list of other minimum high level GMP elements (e.g., qualified personnel, pharmaceutical quality system, training programmes, qualification program of suppliers, etc.) (2.6).

Step 2. Determination of excipient manufacturer's risk profile (Chapter 2)

The MAH should perform a gap analysis (audit, information received from excipient manufacturer): determined appropriate GMP vs. activities and capabilities of the excipient manufacturer.

If relevant, the certification of quality systems held by excipient manufacturers should be considered.

In addition, the MAH should perform a risk assessment to determine **the risk profile of the excipient manufacturers** (e.g. as low, medium or high risk).

Step 3. Confirmation of application of appropriate GMP/Ongoing risk review (Chapter 3)

Mechanisms and procedures should be established in order confirm the correct application of appropriate GMP. Examples of indicators are listed: analysis of defects, trend analyisis of excipient quality, monitoring of changes at the excipient manufacturer level, etc.

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

EFFA Secretariat wants to monitor the potential impact of the COM Guidelines on the activity of companies providing flavouring to the pharmaceutical industry. **Please, send any feedback to EFFA Secretariat.**

If you have further questions, please do not hesitate to contact EFFA at info@effa.eu or your respective national association.

EFFA Secretariat – 13 May 2015

Enclosures: 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 (FL/15/17)

[1] According to Article 5.1. of Regulation (EC) No 852/2004, "Food business operators shall put in place, implement and maintain a permanent procedure or procedures based on the HACCP principles".