Introduction

- Impact on pharmaceutical excipient makers, distributors & users
- EU Risk Assessment Guidelines (draft)
- EU-GMP Guidelines Part I Chapter 5 (draft revision)
Falsified Medicines Directive 2011/62/EU:
key information

- Designed to prevent the infiltration of fake medicinal products within the legal distribution chain in Europe
  - Published in the Official Journal 1st July 2011
  - Deadline for transposition of the Directive 1st January 2013
  - Date of application of certain provisions 1st July 2013
- Deadline for implementation of the certain provisions 36 months after publication of the delegated act


Falsified Medicines Directive 2011/62/EU:
Active Pharmaceutical Ingredients - API

Key points:
- API producers based in Europe must register their activities, and notify of any changes to the authorities
- Imported APIs must comply with GMPs equivalent to EU-GMP Part II Guide; a list of approved countries will be available
- Imported APIs have to be accompanied by a GMP confirmation of the Third country (if not listed)
- Market authorization holders (MAH) will have to conduct audits of their suppliers (manufacturers and distributors), and verify GMP and GDP
- GDP Guidelines to be adopted by the EU Commission (draft published in February 2013)

Important note: some excipients may be used as API, so these changes have to be considered, but “Atypical APIs” may be considered differently.
Falsified Medicines Directive 2011/62/EU: Excipients

Rationale:
- Risks in the pharmaceutical supply chain are not just API related, excipients may impact
- Regulators expect Market Authorization Holders to secure their supply chain

How to address this:
- by implementing the appropriate level of GMP
- Application of risk management
- by means of periodical, physical audits
- Related changes to EU-GMP Guidelines Part I (chapter 5)

➢ And yet the emphasis in the FMD is on GMP

Falsified Medicines Directive 2011/62/EU: Key clauses

Art. 46 f
The holder of the manufacturing authorization shall ensure that the excipients are suitable for use in medicinal products by verifying the appropriate good manufacturing practice on the basis of a formalized risk assessment. In this risk assessment, the holder of the manufacturing authorization shall take into account the source and intended use of the excipients and previous incidents.

Art. 47
Guideline for a formalized risk assessment and verification of appropriate GMP for excipients shall be adopted by the Commission in accordance to Art 46 f. (draft 05.02.2013)

Excipient are in the scope of the directive and have now a definition:
- Any constituent of a medicinal product other than the active substance and the packaging material

Use of Risk assessment to define appropriate GMP to be applied by excipient suppliers

Inspections by authorities at an appropriate frequency based on risk at premises of
- manufacturers or importers of excipients
- EU and Third countries
- can be unannounced

Art. 111

... inspections at an appropriate frequency based on risk...of manufacturers, importers, or distributors of active substances...and effective follow-up

Whenever it considers that there are grounds for suspecting non-compliance with the legal requirements...competent authority may carry out inspections at the premises of:
- (a) manufacturers or distributors of active substances located in third countries;
- (b) manufacturers or importers of excipients.
Manufacturers to ensure appropriate GMP compliance of excipients following risk assessment in accordance with guidelines to be produced by the Commission.

Elements of Risk assessment shall take into account:
- requirements under other appropriate quality systems
- source and intended use of the excipients
- history of quality defects ("incidents")

Manufacturing Authorization holder has to verify that these appropriate standards of GMP are applied and documented.

EC Draft Guidelines on the formalised risk assessment

- Published on 5th Feb. 2013 for consultation until 30th April 2013

- 4 Sections:
  - Introduction
  - Determination of appropriate GMP based on type of excipient
  - Determination of excipient manufacturer’s risk profile
  - Confirmation of application of appropriate GMP

- Introduction
  - The excipient risk management procedures should be incorporated into the quality management system
EC Draft Guidelines section 2

“Determination of appropriate GMP based on type of excipient”

- ICH Q9 provides principles and examples of tools
- Quality Risk Management principles to assess risk to quality, safety and function of each excipient
- Excipient classification into “low risk”, “medium risk”, and “high risk”
- Identify risks from excipient source (animal, mineral, vegetable, synthetic etc.). Areas to consider:
  - TSE, Viral, microbial, endotoxine contamination
  - Impurities from raw materials and process
  - Sterility
  - Use of dedicated equipment
  - Environmental controls

Areas to consider related to function of each excipient:

- The pharmaceutical form and use of the medicinal product
- The function of the excipient in the formulation
- The quantity used of the excipient in the 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
Define elements of GMP (e.g. from EU-GMP Part I and II) to be in place and consider as a minimum:
- Effective Quality Assurance System
- Sufficient competent and appropriately qualified personnel
- Defined job descriptions for managerial and supervisory staff
- Training programmes for all staff involved in manufacturing and quality
- Training programmes related to health, hygiene and clothing
- Provision and maintenance of premises and equipment
- Documentation system for all processes and specifications including retention of batch documentation for at least one year after the expiry date
- Systems to allow full traceability
- Independent quality control department
- Retention of records for starting materials and excipients, retain samples
- Written contracts for contracted services
- Complaint and recall system
- Regular self-inspection programmes
- Non-GMP measures required to manage the identified risk

A documented gap analysis of the required GMP against the activities and capabilities of the excipient manufacturer
- Data/evidence through audit or from information
- Quality system certification or accreditation according to GMP
- Risk assessment to determine the risk profile (i.e. low risk, medium risk or high risk, for that excipient manufacturer).
- Use ICHQ9 to classify the risk profile of the excipient manufacturer an apply tools mentioned there (e.g. HACCP).
- Series of risk mitigation strategies ranging from acceptance through control to unacceptance
- Control strategy (e.g. audit, document retrieval and testing) should be established.
After definition of „appropriate GMP“ perform on-going risk review:

- Number of defects on received batches
- Type/severity of defects
- Loss of relevant quality system accreditation
- Observation of trends in drug product quality attributes
- Audit (re-audit) of excipient manufacturer

EC Draft Guidelines section 4

“Confirmation of application of appropriate GMP”

Draft EU GMP Guidelines Part I

Chapter 5 (Production)

Published Feb. 2013 for consultation until 18th July 2013

- Starting Materials:
  - 5.26
    - Stricter controls and supervision over the entire supply chain of starting materials (risk based)
    - Appropriate aspects to be documented in quality agreements or specifications
  - 5.27
    - Audits of suppliers of excipients with a particular risk

- 5.33 Requirements in case of reduced incoming testing
  - Supplier audits (Compliance with GMP and test methods)
  - Formal agreement in place (contract testing)
Thank you for your attention:
Questions?

Acknowledgement:
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