



GMP Aspects of Excipient Supply a risk based approach

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GMP Aspects of Excipient Supply

- Excipient production processes
- What is appropriate excipient GMP?
- Risk assessments



GMP Aspects of Excipient Supply

- Directive 2011/62/EU (Falsified Medicines Directive) gives the first legal definition of 'excipient'



GMP Aspects of Excipient Supply

- Directive 2011/62/EU (Falsified Medicines Directive) gives the first legal definition of 'excipient'
- *Any constituent of a medicinal product other than the active substance and the packaging material*

GMP Aspects of Excipient Supply

- Excipients are a diverse collection of materials from many origins
- Over 1200 excipients are in use in marketed pharmaceutical products (not including colours & flavours)
- Only about 300 to 400 currently have monographs in various pharmacopoeia

- Function in a pharmaceutical dosage form varies widely:
 - simple filler/diluent in a hard gelatine capsule
 - solubility enhancer for a poorly soluble drug
 - rate controlling polymer in a modified release system



Petrochemicals

- macrogol
- iso propanol
- propylene glycol
- methacrylates
- poloxamers



Agriculture



- starches
- dextrans
- cyclodextrin
- cellulosics
- sucrose
- alginates

Minerals

- talc
- titanium dioxide
- calcium phosphate
- kaolin



Animals

- lactose
- shellac
- gelatine



Plus increasing use of biotechnological processes



GMP Aspects of Excipient Supply

- Excipient GMP must be applicable to a diverse range of manufacturing processes
- Everything from mining and milling to complex chemical processes
- Must accommodate continuous processes

GMP Aspects of Excipient Supply

- Most materials used as excipients have their majority use in other industries, ranging from food and cosmetics but also including construction
- *total cellulose production is approx. 250 million tonnes / annum*
- *cellulose products use in pharma is approx. 50,000 tonnes / annum (0.02% of total)*

GMP Aspects of Excipient Supply

What is appropriate GMP for excipients?



- IPEC GMP Guide 2001 published to help standardize expectations.

GMP Aspects of Excipient Supply

- European Directive 2011/62/EU requires **manufacturing** authorisation holders establish that the excipients they use are made according to *appropriate GMPs*
- Based on a formal risk assessment using guidelines published by Commission in March 2015
 - To be completed by 21 March 2016
 - The holder of the *manufacturing authorisation* shall document the measures taken



GMP Aspects of Excipient Supply

- The risk assessment is comprised of three distinct phases:

Risk Assessment Phase One

- **Determination of appropriate GMP based on type and use of excipient**
 - excipient itself
 - how it is used
- From these two factors it is necessary to determine which elements of GMP need to be in place to control and maintain quality
- References include Annex 1 or/and Annex 2: Part II Basic Requirements for Active Substances used as Starting Materials

Risk Assessment Phase Two

- **Determination of excipient manufacturer's risk profile**

- Perform a gap analysis between the determined appropriate level of GMP against the capability of the manufacturer
- Use data from an audit or information from the manufacturer
- Take into account any certification against appropriate standards
- Any gaps identified should be documented and a mitigation strategy implemented

Risk Assessment Phase Three

- Confirmation of application of appropriate GMP**

- After the appropriate level of GMP and the risk profile of the manufacturer have been defined then an ongoing risk review needs to be performed
- Using for example monitoring and trend analysis of excipient quality, type and severity of defects, changes control at the manufacturer



GMP Aspects of Excipient Supply

- The International Pharmaceutical Excipients Council (IPEC) identified many years ago that excipient GMP needs to be separated from API GMP
 - Published a specific GMP guide for excipients



The
Joint
IPEC – PQG



FOR
PHARMACEUTICAL
EXCIPIENTS



2006



IPEC Resources

- New IPEC Europe 'How-To' Document on the EU Guidelines of 19 March 2015 (OJ 2015/C 95/02).
- The document was collaboratively developed by member company representatives (including excipient makers, users, and distributors).

The screenshot shows the IPEC Europe website. At the top, there's a navigation bar with links for Home, Members, Board, Committees, Publications, Events, Procedures, IPEC Federation, and Info. Below the navigation is a banner for "The International Pharmaceutical Excipients Council Europe" with the tagline "Helping To Shape The Future Of Excipients". The main content area has two columns. The left column contains a "WELCOME, COLORCON" message with a "Logout" link, and a "PROJECT ROOM" section with a "Click here to access to the platform" button. The right column contains a large image of various pharmaceutical tablets and capsules, followed by the text "IPEC Europe Supporting the interests of pharmaceutical excipient developers, producers, distributors and users." Below this are sections for "Home > Publications > Guidelines Guidelines" and "IPEC Guidelines". A sidebar on the right provides download links for various documents.

IPEC Europe
Supporting the interests of pharmaceutical excipient developers, producers, distributors and users.

WELCOME, COLORCON
You're logged in
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Click here to access to the platform

IPEC Europe
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Home > Publications > Guidelines
Guidelines

IPEC Guidelines

The IPEC guidelines can be downloaded here:
2016 The IPEC Europe 'How-To' Document on EU Guidelines on Risk Assessment for Excipients
> Download PDF Format

2014 The IPEC Glossary of Terms
> Download PDF Format



GMP Aspects of Excipient Supply

- Now the guide has been supplemented by a standard for excipient manufacture GMP
- Excipient companies can now be inspected and certified as meeting this standard
- 22 EXCiPACT certificates issued to date



international excipients certification



Summary

- The requirement for pharmaceutical companies to conduct these risk assessments for each excipient used, creates a large amount of work requiring a considerable resource allocation
- Deadline for completion: 21 March 2016 **Passed**
- Possible this will discourage innovation and the preference will be to use previously risk assessed materials
- IPPEC/EXCiPACT tools could potentially reduce some of the burden