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’

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- *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

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Petrochemicals

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

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Agriculture

- starches
- dextrins
- cyclodextrin
- cellulosics
- sucrose
- alginates

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Minerals

- talc
- titanium dioxide
- calcium phosphate
- kaolin

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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

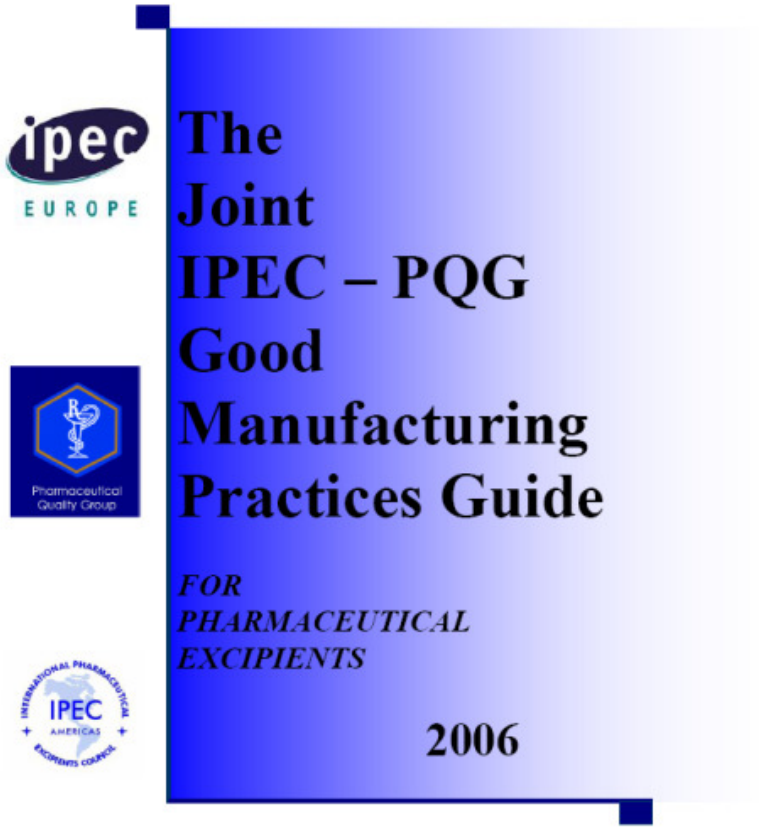
- **Determination of excipient manufacturer's risk profile**
  - Perform a gap analysis between the determined appropriate level of GMP against the capability of the manufacturer
  - Use data from an audit or information from the manufacturer
  - Take into account any certification against appropriate 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

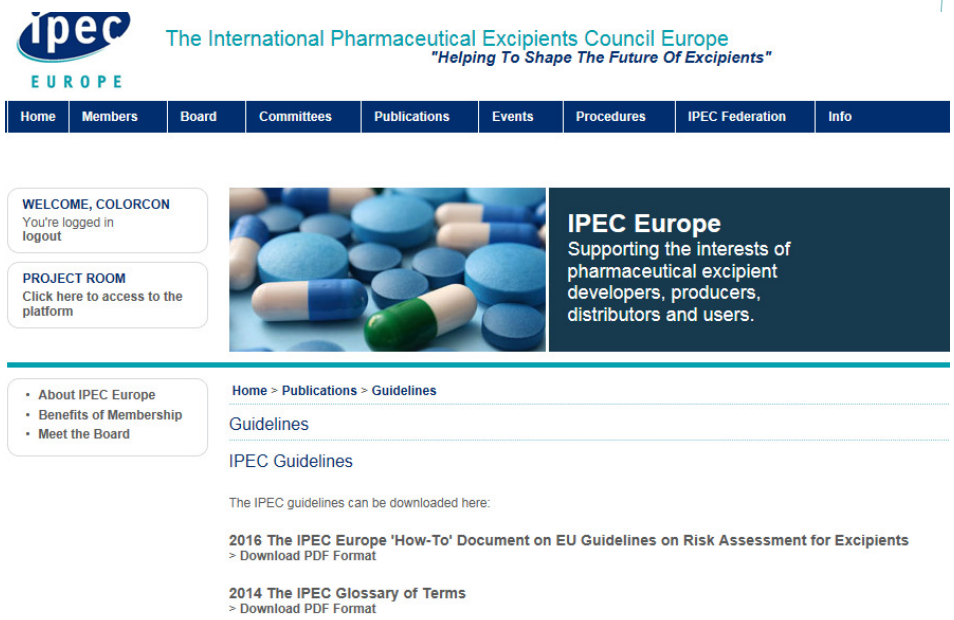
- The International Pharmaceutical Excipients Council (IPEC) identified many years ago that excipient GMP needs to be separated from API GMP
- Published a specific GMP guide for excipients



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).



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
- IPEC/EXCiPACT tools could potentially reduce some of the burden