The Joint IPEC-PQG GMP Guide for Pharmaceutical Excipients
Content, Application and Benefit for Industry

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Good Manufacturing Practices for Pharmaceutical Excipients

- How is excipient manufacture regulated?
- What is appropriate GMP?
- Role of the IPEC/PQG guide
- Future plans
What is an excipient?

- 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
How is excipient manufacture regulated?
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- To the surprise of many the manufacture and supply of excipients is unregulated by any agency.
- European legislation puts the onus on the user, the MA holder to ensure that starting materials are of a ‘suitable’ standard.
How is excipient manufacture regulated?

- The European Pharmacopoeia General Monograph 2034 states:
  - *Substances for pharmaceutical use are manufactured by procedures that are designed to ensure a consistent quality and comply with the requirements of the individual monograph or approved specification.*
How is excipient manufacture regulated?

- There is no official designated GMP standard to apply
- Expectations from pharmaceutical companies are very diverse
- Users apply their own standards based on a variety of sources
What is an excipient?

- Most materials used as excipients have been ‘borrowed’ from other industries
- For example magnesium stearate, very commonly used as lubricant in tablet production finds its main use as a mould release agent in the plastics industry
What is an excipient?

- 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 approximately 250 million tonnes / annum*
  - *Cellulose products use in pharma is approximately 50,000 tonnes / annum (0.02% of total)*
What is an excipient?

Sources

- Petrochemicals
- Agriculture
- Minerals
- Animals
- Biotechnology
What is an excipient?

• Processes may be very simple or very complex
• Including:
  – Mining & milling
  – Physical processes
  – Very large scale
  – Continuous processing
  – Blended and Co-processed products
Good Manufacturing Practices for Pharmaceutical Excipients

(5) The licence holder shall ensure that:

(a) excipients are suitable for use in a medicinal product by:
   (i) ascertaining what the appropriate good manufacturing practice is, and
   (ii) ensuring that the ascertained good manufacturing practice is applied;

(b) the suitability of the excipient is ascertained on the basis of a formalised risk assessment as described in paragraph 5 of Article 47 of the 2001 Directive;

(c) the assessment under sub-paragraph (b) takes account of:
   (i) the source,
   (ii) requirements under other quality systems,
   (iii) intended use of the excipients, and
   (iv) previous instances of quality defects;

(d) the authenticity and quality of any excipient used is verified; and

(e) the measures taken under this paragraph are documented by the licence holder.
How is excipient manufacture regulated?

- With such a diverse range of sources, manufacturing methods and intended markets, can a single set of cGMP standards be suitable for all?
- By comparison, Finished Dosage and API manufacture is much more focused in terms of manufacturing methods and intended use.
Compliance standards

- ISO 9001:2008
- EU GMP for APIs (Eudralex vol IV part 2)
- 21 CFR parts 210 and 211
- HACCP
- GMP for finished pharmaceuticals
What is appropriate GMP for Excipients?

- 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
What is appropriate GMP for Excipients?

- Soon after its formation in 1991, IPEC identified a need for GMP guidance specific to excipients
- To create a level playing field for stakeholders
- To use as a tool for both manufacturers and users
What is appropriate GMP for Excipients?

- In 1995, IPEC published:
  - Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients
  - Joint publication between IPEC America and IPEC Europe
• The principles adopted, which remain today is that the publication is a voluntary guidance only not a standard

  – Consistent use of the term ‘should’ not ‘must’

  – Use the format and paragraph numbers of the ISO 9000 series of standards (ISO9002 July 1994 at the time)
1995 IPEC Guidance

• The content included a complete quality management system, with enhanced detail to cover
  – Process control
  – Inspection and Testing
  – Handling, Storage, Packing, Preservation and Delivery

• Care was taken not to be over-prescriptive, but to accommodate best practice to ensure suitability in terms of quality, purity and safety
Revisions since 1995

• In 2001

• New revision, aligning the layout with ISO9001:2000

• Adding new sections in line with the ISO standard, eg continuous improvement
Revisions since 1995

• In 2006
  • Working with the Pharmaceutical Quality Group the guide was combined with the PQG PS9100:2002
  • Combined with WHO GMP guidelines
  • Retitled
    – *The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients*
Working with regulators

- Throughout the development, revision and launch of the guidelines, dialogue with US and EU regulatory bodies was maintained.

- The guide was included in Pharmeuropa (9.2 June 1997 as a general information article).

- The content of the guide is included in the current USP/NF as General Chapter <1078>. 
Industry reaction

• In general the guide is ‘unofficially’ used as an industry standard document

• Many pharmaceutical customers use the guide as the basis for their inspection of their excipient suppliers

• The guidance is often cited in supply quality agreements
In 2012 the launch of EXiPACT has now resulted in the availability of a certifiable standard for the manufacture, supply and distribution of excipients.

The role of the guidance document needs to change to align with this standard.
Future revisions

• The Joint IPEC/PQG guide has just entered into a revision phase

  – to align with the EXiPACT standard
  – to adjust the format with ISO9001:2015
Future revisions

• Intention is to
  – include more examples to illustrate various principles
  – include guidance on various topics, eg risk assessment

• The target date for publication of the revised guide is December 2015
THANK YOU!