Excipients - Supplier View

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Presentation Outline

- Relevance and Scope
- Regulatory Background
- Difficulties and Challenges in Regulating Excipients
- Excipients GMP & GDP Certification Project
Are Excipients a Risk Factor?

- Critical incidents caused by Excipients have cost too many lives
- Reasons for such incidents were unintended or intended activities resulting in contaminated Excipients
- Main risk elements related to Excipients are
  - Intransparent Excipient pedigree
  - Reduced testing and inappropriate testing methods
  - Lack of knowledge about supplier premises and processes
  - Lack of knowledge about the intended use of the Excipient
  - Inadequate equipment and handling in the supply chain
Excipient Supply Chain

Excipient Producer (GMP/ non-GMP)

Certificate

Contractor

Trader

Sourcing Services

Distributor

• Warehousing
• Repacking
• Services

Drug Producer

Certificate

Certificate
Excipient Expectations

Regulator
- Compliance with various different national and global standards

Producer
- ROI, Application
- ...

Distributor
- ROI, Documentation
- ...

Drug Producer
- Functionality, Quality, Low Cost, Different pack sizes, GMP, USP/EP/BP ...

Excipient
- Safety

Patient
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Regulators reaction on past incidents (Panama, China)

Guidance for Industry “Testing of Glycerin for DEG*”),
May 2007 (http://www.fda.gov/cder/guidance/7654fnl.htm)
- DEG testing of samples from each container
- Knowledge about the supply chain ("manufacturer and any subsequent distributor")
- Repackers and distributors should test glycerin
- Application of cGMP by suppliers of glycerin
- Similar recommendations/requirements for other excipients

Guidance as Q&A on EMEA website
- Testing of each container for DEG applying Ph. Eur. Method
- Companies should consider glycerol as a "higher risk material"
- Application of risk management in the supply chain
- Inspectors focus on qualification of supply chain of glycerol

* Diethylene Glycol
Current Regulation in Europe

- Article 46 (2004/27/EC)
  The holder of a manufacturing authorization shall at least be obliged:
  f) To use only active substances employed as starting materials which have been manufactured in accordance with detailed guidelines on good manufacturing practice for starting materials.
  This point shall also be applicable to certain excipients, the list of which and the specific conditions of application shall be established by a Directive...

- Article 46a
  For the purpose of this directive, manufacture ... shall include ... the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labeling, such as carried out by a distributor of starting materials,...

Manufacturers and distributors of “certain excipients” will have to apply GMP in their operations!
Current Regulation in the USA

- Food, Drug and Cosmetic Act (Section 201, „Definitions“)
The term "drug" means :(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and......

- Food, Drug and Cosmetic Act (section 501(a)(2)(B))
A drug or device shall be deemed to be adulterated if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;....
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Difficulties and Challenges in Regulating Excipients (1)

• No explicit requirement for GMP for Excipients
• Different awareness of specific pharma requirements amongst Excipients manufacturers
• The supply chain often involves distributors or traders
• Excipients pose a potential risk to the patient
• If the pharmaceutical manufacturers controls are compromised then this risk can be realised
• More than 1000 Excipients in use
• Pharmaceutical manufacturers are struggling with comprehensive
  - Supplier qualification, supplier audits and testing on delivery
• Recent events highlight some of the weaknesses in the supply of Excipients
• Pharmaceutical user Audits are important but infrequent/incomplete
• Can regulators and drug manufacturers inspect ALL Excipient suppliers?
Difficulties and Challenges in Regulating Excipients (2)

- Recent signals from the EU and FDA have indicated that:
  - 3rd Party Excipient Audits and Certification have a role to play
  - For APIs The December 2008 Pharmaceutical Package from the EU expressly required this

- A one size fits all approach to GMP is difficult, either the bar is too high or it is too low….

- GDP (Good Distribution Practice) needs to be included

- Ways have to be found to engage the entire Excipient industry despite its diversity
How to approach Excipients Regulation?

- EFCG promoted the development of a global task force to provide a solution which led to a memorandum of understanding with IPEC in May 2008
- GMP and GDP Certification is a daunting task and even IPEC or EFCG alone cannot hope to deliver a global solution
- The partners bring their experience and expertise to the overall project which will be global in scope
- IPEC Europe and EFCG Partners now include:
  - FECC - European Association of Chemical Distributors
  - IPEC - Americas
  - PQG - Pharmaceutical Quality Group
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Excipients GMP & GDP Certification Project
Experience with GMP & GDP Certification

- Past Experience with PQG PS 9100
  - Use ISO 9001 type auditing and certification
  - Only 2 certificates have been issued - both in the UK
- IPEA - International Pharmaceutical Excipients Auditing Inc
  - Uses expert audit report (comparable with regulatory inspection)
  - More uptake than PS 9100 and worldwide in scope
- EFfCI GMP Guide for Cosmetic Ingredients
  - Scheme launched November 2008 – ISO 9001 type certification
  - IPEC-PQG GMP Guide is 80% identical to the EFfCI GMP Guide

Use experiences of these to build Excipients Certification Programme
European Excipients Certification Project

Key Deliverables of the Project:
- International in scope
- Based on the IPEC-PQG GMP Guide 2006
- Based on IPEC GDP Guide 2006
- Aligned to ISO 9001 (2000 and 2008 editions)
  - Many Excipient suppliers are already ISO certified

Key Project Principles:
- Evolve existing best practices from all known sectors
- Classify Excipients
- Must include GDP and GMP
- Auditor training and competency requirements must be defined
- The scheme must apply to the majority of the existing Excipient industry without raising the bar too high
Why classify Excipients?

- They have many diverse uses, functions, manufacturing processes and origins
- So the risks posed to the patient are also very variable
- Hence a one size fits all definition of GMP is not going to be enough
Excipient Classification

THOROUGHNESS OF GMP IMPLEMENTATION
(PRINCIPLES TO FULL PHARMACEUTICAL GMP)

IPEC-PQG GMP GUIDE

Class 2
Class 1
Class 3

RISK TO PATIENT
(ROUTE OF ADMINISTRATION)
Excipient Classes (1)

- The classification will define the extent of GMP required,
  - Recent survey conducted by IPEC Europe to see what users and suppliers in the trade associations thought about this concept

- The IPEC-PQG GMP Guide will be the foundation (class 1)
- The highest class (3) should not exceed EU Part II / ICH Q7 GMP
- An intermediate class (2) between these should be defined (Investment in the quality management system is high)
Expectation of Class Repartition

Source: survey by IPEC Europe
Classification Process

1. Manufacturer to perform risk assessment, and so determine class of GMP
   • Supplier to communicate GMP class to Suppliers and Users (e.g. on CoA)
2. User to perform risk assessment and request GMP class from supplier
   • User to communicate GMP class to suppliers at contract review
3. User and Supplier to perform joint risk assessment
   • Best option, but may not always be practical due to numbers of customers (1000s) and number of Excipients (1000s)
   • BUT an agreement at least on the GMP class must be part of contract review between the two parties
Key Elements of the Classification risk assessment

1. Known functionality characteristics of the Excipient
2. Known uses of the Excipient including route of Administration
3. Origin of the Excipient (animal, vegetable, mineral)
4. Manufacturing process / Multi purpose plant
5. .....
IPEC-PQG GMP Guide

Lead Members: PQG, IPEC Europe, IPEC-Americas

First Phase GMP Certification
- Will Use the IPEC-PQG GMP Guide 2006
- An Annex to ISO 9001:2008 will be prepared that places additional auditable requirements on a supplier
- Some aspects of the current Guide have been made compulsory as a result
- Enhanced GMP requirements for the other classes of Excipients have been developed
  - A draft of the base GMP and the enhanced requirements are available for comment
Goal of Excipient GMP Certification

• Transform the IPEC-GMP Guide into an ISO 9001 type standard
• ISO 9001 and related Pharmaceutical Packaging (ISO 15738) and Medical Device (ISO 13485) auditors can then be trained to conduct audits of suppliers against these requirements
• Allows access to a large and international pool of auditors
IPEC GDP Guide

Lead Members: FECC, IPEC Europe, IPEC-Americas

- Good Distribution Practices are essential as recent tragedies have illustrated
- IPEC GDP Guide 2006 built on the WHO GDTP Guide 2003 and are integrated with good transportation practices for chemicals
- Excellent uptake of GDP in certain Excipients Consultation
IPEC GDP Audit Guide

- GDP Audit Guide is aligned with the European SQAS ESAD II assessment scheme (www.sqas.org)
  - Which is already subject to independent assessment
  - And has a defined auditor training programme
  - Therefore build on this structure and system to deliver GDP certification using the enhanced definitions of Auditor competency
Key Stages

- Matched to fit the activities in the supply chain
- The GDP aspects should be capable of being audited separately from the GMP part – to distinguish between those organisations who are uniquely distributors or manufacturers
- An Annex to ISO 9001:2008 needs to be developed which sets out the requirements in the GDP Guide. Alignment to the ISO 9001 section headings is currently in progress
Content of IPEC GDP Guide

- Quality management system
- Organisation and personnel
- Warehousing and storage
- Equipment
- Documentation
- Re-packaging and re-labeling
- Complaints and recalls, Returned goods
- Dispatch and transport
- Contract activities
Auditor Competency (1)

Lead Members: to be defined
Whatever “certificate” where do we find all the auditors?
  • Given the numbers of excipient suppliers
  • Given the global reach of certification, mirroring the supply chain
  • Who has enough auditors to perform frequent, at least annual audits of suppliers?
  • IPEA? Inspectorates? Users? Other similar bodies?
  • ISO 9001 pharmaceutical industry auditors?
    ▪ Potentially 1000s of these
    ▪ Well developed and policed accreditation infrastructure
    ▪ Already perform medical device audits
Auditor Competency (2)

- Regulators have consistently stated they have concerns about auditor competency and their ability to perform effective GMP audits
  - Hence project will deliver auditor competency criteria and ensure that auditors are trained in these requirements
- EU December 2008 Pharmaceutical Package stated that:
  - The user must verify compliance to GMP/GDP by themselves or through a body accredited for that purpose by the competent authority of a Member State.
  - But APIs only (excipients are not mentioned in this draft Directive)
Auditor Competency Requirements

• Will cover GMP and GDP aspects
• Need to access as many auditors as possible
• Training materials will be made available for auditors
• To further enhance matters in this area an individual auditor accreditation system is desirable
• It will define auditor competency and pedigree
• European regulators invited to participate
• What else do we require on this topic?
How does the Certification work?
Current Status of Certification Project

- An ambitious project has been defined and launched
- The key components have been defined
- Task forces and their deliverables have been assembled and are making excellent progress
- Participants have been invited and calls made to ask for volunteers
- Feedback will be sought at key stages in the development of the project
Reactions to Certification Project

- Publicity and Advocacy
  - Presentation of scheme was given to EMEA Interested Parties meeting in London 26 November 2008
  - The scheme was observed as “ambitious”
  - “A good idea” in that it will increase assurance of the pharmaceutical starting material supply
- Details have been given to the FDA recently. Feedback awaited
Thank you for your attention!

and

To the contributors to this presentation

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