NSF/IPEC/ANSI 363: Good Manufacturing Practices (GMP) for Pharmaceutical Excipients

Multiple stakeholders; one objective.

Presented by Janeen Skutnik-Wilkinson

International Pharmaceutical Excipients Council
Collaborative solutions for excipient industry stakeholders

Setting the Scene

- FDASIA: 2012: Sec. 711: Enhancing the safety and quality of the drug supply
  - Redefines meaning of cGMP:
    - “Includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing role of and establishing the safety of raw materials, materials used in the manufacture of drugs and finished products”

- FMD: 2011: Article 46f:
  - “The holder of the manufacturing ensure that excipients are suitable for use in medicinal products by ascertaining the appropriate GMPs”

- EU Chapter 5: 5.29
  - “..... The following is required: Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment in accordance with the EU Commission “Guidelines on the formalised risk assessment for ascertaining the appropriate GMP for excipients...”"
National Technology Transfer & Advancement Act (1996)

- Requires federal agencies adopt private sector standards, particularly those developed by standards developing organizations, wherever possible, in lieu of creating proprietary, non-consensus standards.
- Goal is to reduce unnecessary government standards that create confusion and add expense for compliance.

OMB Circular A119 (1993)

- “Federal Participation in the Development and Use of Voluntary, Consensus Standards and in Conformity Assessment Activities.”
- Establishes policies for Federal use and participation in consensus standards and on conformity assessment activities.
- Revised in 1998 to achieve consistency with NTTAA terminology.

NSF/IPEC/ANSI – 363
2014 GMP for Pharmaceutical Excipients

- Achieve Excipient Realization
  - Implement and maintain a system that delivers excipients with quality attributes that meet the needs of:
    - Customers
    - Regulators

- Establish and maintain a state of control
  - Ensure manufacture & supply is in accordance with the standard.
  - Provides customers with some assurance of quality, continued stability and reliability of supply.

- Facilitate continual Improvement
  - Collect objective evidence to continually develop and enhance the application of QMS principles to further assure excipient consistency.
EXCiPACT asbl

- EXCiPACT™ is a voluntary third party certification scheme for excipient suppliers.
- The EXCiPACT GMP Standard and the ANSI NSF 363 GMP standard for pharmaceutical excipients are equivalent.
  - The small differences will be eliminated at the next revision of the EXCiPACT GMP Standard in 2015

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NSF/IPEC/ANSI 363

- IPEC-PQG GMPs (2006)
- NSF/IPEC/ANSI 363 or EXCiPACT
  - meets the expectations in FDASIA, and FMD & EU Excipient Risk Assessment Guideline.
  - Provides an Auditable Standard.
- Quality Risk Management
  - Incorporated throughout the standard
  - 21 Clauses call out requirements around Risk
  - Provides flexibility
- Implementation
  - An IPEC Risk Assessment Guide being developed to use with this standard to assist in implementation.
What’s in it for....... 

Excipient Manufacturers 
- Consistent approach to GMPs 
- Standard to be audited to 
- Marketing advantage 
- Level playing field

Pharmaceutical Manufacturers 
- Unified, auditable standard to ensure GMP compliance and consistency 
- Key part of supplier qualification & monitoring 
- Supports implementation of FMD & FDASIA

Regulators 
- Standards for excipient GMPs 
- Consistency 
- Supports new and emerging regulations

IPEC-America’s Recommends

Excipient Manufacturers = IMPLEMENT 
Pharmaceutical Manufacturers = ADOPT 
Regulators = ACCEPT
Excipient Manufacturers Implementation

Current state of conformance to IPEC-PQG GMPs

Complexity of excipient(s) produced

Dependant upon:

Number of excipients produced

Resources for updating QMS

Excipient Manufacturer Implementation

Review Standard

Review project plan with Management and gain approval

ID activities required for conformance

Create implementation plan for each site by end of 3Q2015

ID clauses where QMS is not in conformance (Gap Assessment)

Establish project plan with timeline for each activity

Prioritize activities to implement 363

Cross Functional Team to develop a plan to resolve gaps

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- Assess operations to identify applicable requirements
- Unopened original excipient packaging: fewer items apply
- Repackage: consider actions under excipient manufacturers

Pharmaceutical Manufacturer’s Adoption

- Provides a single, auditable standard
  - Jointly developed by pharmaceutical manufacturer’s, excipient manufacturer’s, FDA and Academia.
- Provides clarity and consistency
- Consider revising practices to incorporate expectations for conformance to 363
From IPEC-PQG → NSF/IPEC/ANSI 363

- Changes in Regulatory landscape
- Significant focus on Risk called out in NSF/IPEC/ANSI 363
- Much of the high level structure and content of IPEC-PQG Excipient GMP guide Remains

Why Quality Systems?

- No amount of regulatory inspection or analytical testing by themselves can ensure the integrity or quality of a finished drug product (or ingredient used in the drug product).
- Robust quality systems are required to provide this assurance.
- Evaluation and oversight of vendors included in the pharmaceutical supply chain is a critical element of a drug product manufacturer's quality system.
### Basic Elements of Excipient GMP

- **Quality Management System**
  - Quality manual
  - Document & record control
  - Change control

- **Management Responsibility**
  - Commitment to customer
  - Quality policy & objectives
  - Management system planning
  - Responsibilities & authority
  - Management review

- **Resource Management**
  - Employee competence & hygiene
  - Infrastructure & equipment
  - Work environment

- **Manufacturing Process**
  - Planning
  - Communicating with customers
  - Sourcing starting materials
  - Manufacturing & packaging
  - Storage & delivery

- **Monitoring Analysis, and Improvement**
  - Customer satisfaction
  - Internal audit
  - Process and product monitoring
  - Laboratory controls
  - Finished product release
  - Control of failures
  - Corrective/preventative action
  - Analysis of data for improvement

### Quality Management System (QMS) Expectations

- **Quality Management System**
  - Elements should be appropriate and proportionate to each stage of the lifecycle.
  - Maintain and continually improve QMS
    - Using QRM where useful and appropriate
  - Using QRM to identify items that may pose a risk to consistent physical, chemical and/or microbiological excipient quality.
    - Activities, processes, operations
Excipient GMPs

- **Documentation**
  - System & Procedures for document control
  - Quality Manual

- **Change Control Process**
  - Establish and maintain procedures to evaluate and approve changes that may impact quality of excipient.
  - Final approval should be done by department independent of production.

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Excipient GMPs

- **Management Responsibility**
  - Commitment to Quality
  - Quality Objectives, Quality Management Systems Planning
  - Periodic reviews of Quality Management System

- **Appropriate:**
  - Infrastructure
  - Equipment
  - Facilities
  - Training
  - Environmental controls
Excipient GMPs

- **Product Realisation**
  - Understand requirements of end user
    - Compliance with pharmacopoeial requirements
    - Functionality
    - Legal/regulatory requirements

- **Production**
  - Instructions and records required but may differ for type of operation
    - Batch vs. continuous processing
      - Batch: accurate reproduction of appropriate master production instructions
      - Continuous: current processing log should be available

Excipient GDPs

- **Quality Management System should:**
  - Include procedure to verify that any supplier of excipients has the capability to consistently meet requirements.
  - Should include periodic audits.
    - Self or 3rd party
    - Paper audits are no longer acceptable
    - Should inquire if supplier sub-contracts out any part of the process
  - Confirm that the agreed supply chain has been used.
  - Integrity of packaging and seals should be carried out.
Risk Assessments

- Recent Guidance in EU calls for the pharmaceutical industry to conduct risk assessments for the excipients they use.
- **REQUIRES DIALOGUE** with supplier to ensure accurate representation of the risks associated with:
  - Manufacturing
  - Supply of material

ANSI/NSF/IPEC 363-2014 Excipient GMP Standard

**Where is Risk Assessment called for in NSF/ IPEC/ANSI 363?**

- **4.2.1 General**
  ...the Quality Management System shall have a documented risk assessment that defines as if/where appropriate clauses in the standard are incorporated.

Areas where risk assessment is called for in standard:

- 4.3 Change Control
- 5.5.3 Internal Communication
- 6.2.3 Hygienic Practices
- 6.3.1 Buildings and Facilities
- 6.3.3 Utilities
- 6.4 Work Environment
ANSI/NSF/IPEC 363-2014 Excipient GMP Standard

Continuation from last slide

- 6.4.1 Air Handling
- 6.4.2 Controlled Environment
- 6.4.3 Cleaning and Sanitary Conditions
- 6.4.4 Pest Control
- 6.4.7 Washing and Toilet Facilities
- 7.4.1 Purchasing Process
- 7.5.5.1 Raw Material Packaging Systems
- 7.5.5.2 Excipient Packaging Systems
- 8.3.2 Reworking

Is an Excipient fit for use?

Excipient User
- Route of Administration
- Function of excipient

Excipient Manufacturer
- QMS
- Manufacturing
- Supply Chain

- Regulatory Dossier
- Technical Documentation

Risk score rating (low, medium, high)

Risk reduction

Implementation of relevant Quality Practices (GMP/GDP) required

Accept risk

Unacceptable risk

Compliance Monitoring (e.g. KPI/Events/Audit)

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Slide courtesy of Frithjof Holtz, Patricia Rafidison, Stephan Ronninger
See ICH Q9
EXCiPACT™ Certification

ISO 9001 certification

No ISO 9001 certification

EXCiPACT™ GMP / GDP

ANSI NSF 363

EXCiPACT™ Certification

EXCiPACT™ Certification

EXCiPACT™ – minimize risks, maximize benefits

Cost for EXCiPACT™ Audit

Audit fee ~ £9,000
Certificate fee ~ £4,000
Surveillance ~ £4,000

Excipient Supplier

Reduction by one two-day audit a month, plus one day for preparation, at internal cost incl. of ~ £21,000, plus ~£4000 travel expenses per year ~£25,000 savings per year

Pharmaceutical Company

Reduction by one two-day audit a month, plus three days for travel and preparation of the report, ~£36,000 plus travel expenses, ~£16,000 ~£52,000 savings per year

Total cost in 3 years ~ £17,000
Total Savings in 3 years ~ £75,000
Total Savings in 3 years ~ £156,000

Total Industry Benefit £58,000 £214,000

EXCiPACT™ – minimize risks, maximize benefits
EXCiPACT™ - What do the users say?

- “We are obtaining and evaluating any existing 3rd party certification audit reports during the excipient supplier audit planning and preparation process – these are fed into the supplier audit risk assessment process”. Inference: suppliers with EXCiPACT™ Certificates are lower risk...
- The EXCiPACT™ Certificate and Audit Report allowed us to:
  - Increase the audit frequency
  - Spend half a day on site rather than a full audit
- “Helps avoid duplication of effort and can eliminate the need for an audit since each element of the excipient GMP standard is already periodically assessed as part of the 3rd party certification”
- “If an audit is deemed necessary, its scope could then be focused on specific topics that are not already addressed by the certification standard”.

EXCiPACT™ - What do suppliers say?

- “We got major non-conformities raised at the first EXCiPACT audits because we did not do a thorough gap analysis – the requirements for documented risk assessments are “new” cGMPs for excipients”
- “We have saved 6 audits already”
- “The audit was very thorough – at least as good as a regulatory inspection and at the same level as the best customer audits”
- “A customer qualified us using EXCiPACT™ Certification and avoided intercontinental travel”
- “The EXCiPACT™ certificate and the audit report are well accepted by the customers”
- The investment has paid off, customer feedback is very positive!
Richard Andrews from the UK’s MHRA stated:

- “3rd Party certification schemes can assist medicinal product manufacturers in achieving compliance with GMP at reduced cost and impact on time and resource”.

- “Such schemes will also benefit excipient manufacturers as they should reduce the number of audits they are required to host with the consequential reduction in time and cost”.

- “Overall patient safety should be enhanced”

EXCiPACT™ – What do Authorities say?

Dr Steven Wolfgang
APV Excipient Conference Dusseldorf Sept 23rd 2014

FDA and Excipient CGMP
- FDA is a member of ANSI/NSF 363 committee which developing the US excipient CGMP standard
- Basis for the US standard is quality systems and quality risk management
  - ANSI/NSF 363 convergent with Exciapct™ standard
- Manufacturers using a standard like NSF 363 or Exciapct™ to audit suppliers will also have to apply risk management relating to intended use
  - It appears that in many cases 3rd party audits or shared audits will be able to help mitigate most or all of the concerns
Excipient Makers and Users

What we have in common

- Facilities and operations. The maker’s
  - packing area is the start of user’s processing area
  - storage area is the users ingredient storage area
  - finish product testing lab is the user’s incoming ingredient testing lab

- Need to supply
  - The reliability of the maker’s product is the reliability of the user’s drug product supply
  - Supplying product generates cash flow needed to continue operations

- Knowledge
  - The maker knows the excipient
  - The user knows why they use it

The differences

- Makers start with raw commodities consumed by processes to make an excipient
  - Raw materials, Ingredients, Specialty Ingredients
  - Heavy purification and processing to make final product

- Users start with APIs & excipients to make finished products consumed by people
  - Blending, light processing, and packaging

"cGMP for making excipients will be different from cGMP for making finished drugs"

Slide courtesy of Dale Carter

Comments from an Excipient Maker

Economies of scale require standardization within a facility

- Multipliers for incremental cost of operations are large
- Not profitable to make small volume high margin excipients when adding cost to all production

Cost and uncertainty require long range planning

- Large equipment with costly PM programs
- Capital reinvestment with long planning cycle
- Limits on material sourcing (cost & availability)
- Product requirements must be included in long range plans thus need long term contracts

Risk can be passed down the supply chain

- They need to be understood and matched with controls across the supply chain

Productivity in competitive markets limits resources available for audits

- Fix cost targeted at manufacturing and assuring product quality
- There are more customers than audit days – accepting 3rd party audits for basics makes sense

Corporate Modesty

- Intellectual Property versus information needed for Quality/GMP verification
- Many manufacturers start with the same equipment and add operational improvements that provide efficiencies for competitive value
- Don’t go beyond what you need to know – Catalog product versus custom made

Slide courtesy of Dale Carter
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