Excipient Risk Assessment

Richard O’Sullivan - GMP Inspector

GMP Conference

7 February 2017
Dublin
Excipient Risk Assessment-Why?
Excipient Related Product Recall 2016:

<table>
<thead>
<tr>
<th>Identified during HPRA assessment of application of higher strength of formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect benzene specification assigned to carbomer during change control process</td>
</tr>
<tr>
<td>High levels of benzene in finished product formulation</td>
</tr>
<tr>
<td>Company incorrectly identified benzene as a ‘weak mutagen’</td>
</tr>
<tr>
<td>Evaluation of benzene absorption did not factor the use of occlusive dressings</td>
</tr>
<tr>
<td>HPRA toxicological evaluation identified a risk to the patients and a pharmacy recall was initiated</td>
</tr>
</tbody>
</table>
FMD-2011/62/EU

Article 46 Directive 2001/83/EC was amended to include:

“The holder of the manufacturing authorisation shall ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is. This shall be ascertained on the basis of a formalised risk assessment in accordance with the applicable guidelines referred to in the fifth paragraph of Article 47.....”

“The holder of a manufacturing authorization shall at least be obliged:...to verify the authenticity and quality of the active substances and the excipients.”
FMD-2011/62/EU

Article 47 Directive 2001/83/EC was updated to include the following:

“The Commission shall adopt guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients .......”
Content

1. •Background ✔

2. •Guidance ☐

3. •HPRA Expectations ☐
Guidelines

Ch.1: Scope- Identify Excipients

Ch.2: Determine Appropriate GMP Based on the type and use of excipient

Ch.3: Determine Excipient Manufacturers Risk Profile

Ch.4: Confirm Application of Appropriate GMP
Ch.1: Scope

“1.1. ........an excipient is any constituent of a medicinal product other than the active substance and the packaging material.”

“1.2. These guidelines do not cover substances added to stabilise active substances that cannot exist on their own.”
Ch.2: Determine Appropriate GMP Based On The Type And Use Of Excipient

• Risk Profile Your Excipients:
  – Identify the Risks presented to the quality, safety and functions of each excipient from its Source
  – Consider the function and use of the excipients

• Identify the GMP standards that need to be in place to control and maintain the quality of the excipients
Excipient Risk Profile- Excipients Source

- Transmissible Spongiform Encephalopathy
- Viral Contamination
- Microbiological or endotoxin/pyrogen contamination
- Cross contamination (dedicated vs non-dedicated equipment).

- Impurity originating from the raw material (i.e. residual solvents)
- Sterility assurance for sterile excipients
- Environmental control/transport conditions (temperature, humidity for powders)
- Complexity of the supply chain

- Stability of the excipients
- Packaging integrity evidence

07/02/2017
## Excipient Risk Profile - Excipients Use

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form and use of the medicinal product</td>
<td></td>
</tr>
<tr>
<td>Excipients function in pharmaceutical formulation</td>
<td></td>
</tr>
<tr>
<td>Proportion of the excipient in the medicinal product</td>
<td></td>
</tr>
<tr>
<td>Daily patient in take of excipient</td>
<td></td>
</tr>
<tr>
<td>Any known quality defects/adulterations related to excipient</td>
<td></td>
</tr>
<tr>
<td>Is the excipient a composite?</td>
<td></td>
</tr>
<tr>
<td>Potential for excipient to impact the critical quality attributes of medicine</td>
<td></td>
</tr>
<tr>
<td>Any other factors of the excipient that may impact patient safety</td>
<td></td>
</tr>
</tbody>
</table>
Identify GMP Required Standards

- Supplier has an implemented PQS
- Supplier personnel are qualified
- Job descriptions for management and supervisory staff
- Training programmes for all manufacturing and quality staff
- Training in health, hygiene and clothing appropriate for intended operations
- Provision and maintenance of equipment is to appropriate standards
- Appropriate documentations systems covering processes and specifications
- System for coding and identifying starting materials, intermediates and finished products
Identify GMP Required Standards

- Retention of records and samples for appropriate periods of time
- Systems that ensure any outsourced activity is governed by a written contract
- Suitable complaints management system which allows for excipient recall
- Change management and deviation management systems
- Self-Inspection program
- Environmental control and storage conditions
- Qualification programme for suppliers
- System for QC of excipients and batch release performed by personnel independent of manufacturing
Ch.3: Excipient Manufacturers Risk Profile

Perform gap analysis:

- Evidence should be available to support gap analysis
- Are excipients manufacturers quality/GMP systems certified?
- Identify the risk profile of the excipients manufacturer (high, medium, low)

Assign a status to the excipient manufacturer

- Risk profile is: Unacceptable/ Acceptable / Acceptable pending controls
- Procedures should detail this decision process
Ch.4: Confirmation Of Appropriate GMP

Following the initial risk profile, risk review should be ongoing:

- Number of defects relating to excipients batches received
- Type and severity of defects
- Trend analysis of excipients quality
- Loss of GMP/quality certification
- Organisational, procedural or technical changes
- Audit/re-audits, questionnaires

Re-evaluate risk profile

- Should be performed continually i.e. risk profile should be current
Excipient R.A - Summary

1. Identify excipients
2. Risk assessment each excipient based on its source
3. Risk assess excipients based on its function/final formulation
4. Identify the GMP systems required to assure excipients quality
5. Perform gap analysis
6. Identify excipients manufacturer risk profile, and controls required
7. Continual confirmation that appropriate GMP is being maintained.
Content

1. Background ✔

2. Guidance ✔

3. HPRA Expectations □
HPRA Expectations

- Procedures in place as of March 2016
- Clear plan and timeline for implementation
- Excipients RA process should be completed
- Continual review of RA’s is proceduralised
- Incorporation of RA’s into the QMS
Potential Queries/Concerns

- When is it an excipient?
- Do we expected companies to develop their own excipient GMP standards?
- What if a company has a number of suppliers/excipients?
- What do we see as the QP’s responsibility?
- How do the guidelines apply to CMOs?
- Will a supplier qualification system fulfil the requirements of the guidelines?
- What do we expect when an excipient supplier does not respond or participate?
Content

1. Background

2. Guidance

3. HPRA Expectations

07/02/2017
Questions