The Formalized Risk Assessment for Excipients
A Practical Approach

Frithjof Holtz, IPEC Europe Vice-Chair, Merck
Presentation Overview

- Regulatory Background
- EU FMD and Formalized Risk Assessment
- Proposal for Risk Assessment Model
- Summary
Art. 46 f
The **holder of the manufacturing authorization** shall ensure that the excipients are suitable for use in medicinal products by ascertaining the **appropriate good manufacturing practice** on the basis of a **formalized risk assessment**. In this risk assessment, the holder of the manufacturing authorization shall take into account the **source** and **intended use** of the excipients and **previous incidents**.

Art. 47
**Guideline for formalized risk assessment** for ascertaining of **appropriate GMP for excipients** shall be adopted by the Commission in accordance to Art 46 f.


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Guideline on Risk Assessment for Excipients

• EU Commission published 06/02/2013


• Stakeholders are invited to comment on this draft by 30 April 2013 at the latest. Responses should be sent preferably by e-mail to sanco-pharmaceuticals-d6@ec.europa.eu, or by post to Unit SANCO/D/6, DM24 02/050, BE-1049 Brussels.
Risk Assessment Guidelines for Excipients

• The draft guideline is split into three sections
  
  – Determination of Appropriate GMP based on type of Excipient
  
  – Determination of Excipient Manufacturer's Risk Profile
  
  – Confirmation of Application of Appropriate GMP
Determination of appropriate GMP based on Type of Excipient

• For each excipient used the **Manufacturing Authorisation Holder** should **identify the risks presented** to the **quality, safety and function of each excipient from its source** (be that animal, mineral, vegetable, synthetic etc.) through to incorporation in the finished pharmaceutical dose form.

• Recommended that **ICH Q9 principles** are used to assess the risks presented to the quality, safety and function of each excipient and to **classify the excipient** in question as “low risk”, “medium risk” or “high risk”.

Draft Guideline from EC (SANCO/D/6/SF/mg/ddg1.d.6(2013)179263)
Determination of appropriate GMP based on Type of Excipient

- **Areas for consideration** would include:
  - TSE
  - Potential for *viral contamination*
  - Potential for *microbiological or endotoxin/pyrogen contamination*
  - Potential, in general, for any *impurity* originating from the *raw materials* (e.g. aflatoxins, pesticides) or generated as part of the *process* and carried over (e.g. residual solvents and catalysts)
  - **Sterility Assurance** (for excipients claimed to be sterile)
  - Use of *dedicated equipment* and or facilities
  - **Environmental control** and *storage* conditions

Draft Guideline from EC (SANCO/D/6/SF/mg/ddg1.d.6(2013)179263)
Determination of appropriate GMP based on Type of Excipient

• Additionally with respect to the use and function of each excipient the Manufacturing Authorisation Holder must also consider:
  – The pharmaceutical form and use of the medicinal product containing the excipient (e.g. ointment product, injection/infusion etc.)
  – The function of the excipient in the formulation (e.g. lubricant in a tablet product or preservative material in a liquid formulation etc.)
  – The quantity used of the excipient for the manufacture of medicinal products
  – Daily patient intake of the excipient
  – Any known quality defects both globally and at a local company level related to the excipient
  – Whether the excipient is a composite
  – Potential impact on the Critical Quality Attributes of the medicinal product

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Determination of appropriate GMP based on Type of Excipient

- Having established and **documented the risk profile** of the excipient the **Manufacturing Authorisation Holder** should establish and document:

  The **elements of EU GMP** that the **company believes are needed** to be in place in order to control and maintain the quality of the excipient, i.e. The Rules Governing Medicinal Products in the European Union, Eudralex Volume 4, Part I, Annex 1 and Annex 2, Part II etc.

Draft Guideline from EC (SANCO/D/6/SF/mg/ddg1.d.6(2013)179263)
GMP for Excipients

• Manufacturer and user of excipients do not need to develop their own **GMP for excipients**!

• Some examples of **voluntary industry standards**:
  – USP General Chapter <1078>
  – EXCiPACT™
  – NSF/IPEC/ANSI 363-2014 **NEW**

• **The application of these voluntary standards will in most cases be appropriate**
How to implement such a risk assessment?
Industry Approach to Risk Assessment

• A substantial **contribution** to a risk assessment will be needed from the **excipient manufacturer**

• IPEC Europe and PQG are working together to develop a **risk assessment model** for practical application by the excipient user

• The principles are supported by EFPIA
Model proposed

- Industry recognizes that **ICH Q9 does not mandate one specific Quality risk assessment (QRA) tool**, a number of tools are available... and allow application on all affected processes (i.e. also GMP for excipients)

- The industry proposed model is one approach describing the **principle areas** which must be considered by applying any tool to excipients GMP

- The **model fits with existing approaches** to supplier risk management such as the ‘PQG Guide to Supply Chain Risk Management’*
Example Excipient Risk Management Process**

Is an Excipient fit for use?

Supplier/Excipient Identification

Exciipient User
- Route of Administration
- Function of excipient

Risk Identification
- Internal document assessment
- Excipient supplier assessment

Risk score rating (low, medium, high)

Implementation of relevant Quality Practices (GMP/GDP) required

Accept risk

Unacceptable risk

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

Exciipient Manufacturer
- QMS
- Manufacturing
- Supply Chain

• Suppliers information
• Quality/Supply agreement
• CAPA System/Change Mgmt
• Complaint history/recalls
• Audit/inspection results

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Figure 2: Process for risk management to determine the level of GMP/GDP for excipient manufacturing.

- Risk question: Is an Excipient fit for use?
- Identify the current/future excipient (Risk initiation)
- Areas of focus (Risk identification)
- Areas for consideration (Risk analysis)
- Hazards for potential controls (Risk evaluation)
- Select GMP/GDP principles (Risk reduction)
- Deploy appropriate GMP/GDP principles (Risk acceptance)
- Adopt quality management system (Result of the QRM process)
- Compliance monitoring (Risk review)

Existing elements (e.g., ISO 9000)
- IPEC PQG/EXCIPIACT (GMP & GDP guidelines)
- ICH Q7 (PIC/S Part II, EU-GMP Part II)

Best practice
Basis for relevant GMP/GDP principles
Reconsider risk acceptance decision

P. Rafidison, F. Holtz, S. Rönninger,
A Practical Approach of Implementing GMP for Excipients, Pharm. Tech., September, 2014, 26-36
Typical Quality Areas to Consider for the Risk Assessment

- In the context of manufacturing of excipients, **five specific areas of potential risks** should be considered, understood and **assessed** when reviewing the excipient manufacturers’ quality management system, as applicable.

- Quality Management System (QMS)
- Supply chain
- Manufacturing of the excipient
- Route of administration in the drug product
- Function of the excipient

P. Rafidison, F. Holtz, S. Rönninger,
*A Practical Approach of Implementing GMP for Excipients*, *Pharm. Tech.*, September, 2014, 26-36
### Table III: Table of examples as reference for potential hazards and controls.

<table>
<thead>
<tr>
<th>Potential hazards</th>
<th>Potential risk-reduction measure</th>
<th>EXCiPACT (7) use (6) for additional details</th>
<th>ICH Q7 (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What to consider in the assessment?</strong></td>
<td>Examples on how to consider GMP/GDP principles</td>
<td>Chapter</td>
<td>Chapter</td>
</tr>
<tr>
<td><strong>Risk area 1</strong></td>
<td><strong>Elements of the quality management system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management commitment to quality, extend of quality system in place to address GMP measures, appropriate resources aligned</td>
<td>Quality policy, GMP commitment, records of management system review, documented quality review, resources available to fulfil the supply commitment</td>
<td>4.1</td>
<td>17.60</td>
</tr>
<tr>
<td></td>
<td>4.2.1–4.2.2–4.2.3</td>
<td>4.2.1–4.2.2–4.2.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.1</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.2</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Quality and services level management, process and technical capabilities review</td>
<td>Quality agreements, contractual discussion, visits and meetings records; supplier KPI indicators; documentation of frequent discussions</td>
<td>7.2.3, 7.5.2</td>
<td>16.12</td>
</tr>
<tr>
<td>Key quality systems standards and/or credentials</td>
<td>Type of certifications (ISO 9001, Food GMP, hazard analysis and critical control points [HACCP])</td>
<td>Note: EXCiPACT is an ISO 9001 based standard</td>
<td>16.13</td>
</tr>
</tbody>
</table>

P. Rafidison, F. Holtz, S. Rönninger,
A Practical Approach of Implementing GMP for Excipients, Pharm. Tech., September, 2014, 26-36

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### Basic GMP Elements

#### Table I: Basic GMP elements for the manufacturing of excipients.

<table>
<thead>
<tr>
<th>Topic</th>
<th>EC draft (5)</th>
<th>EXCiPACT (7)</th>
<th>ICH Q7 (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>An effective quality assurance system including quality management</td>
<td>11 a</td>
<td>4.1, 4.2, 4.3, 5.0</td>
<td>2.1</td>
</tr>
<tr>
<td>principles and documentation (including ISO 9001 references)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate personal and hygiene</td>
<td>11 b–e</td>
<td>6.2</td>
<td>3.1, 3.2</td>
</tr>
<tr>
<td>Buildings and facilities design fit for purpose and process equipment</td>
<td>11 f</td>
<td>6.3, 6.4</td>
<td>4.1, 5.1</td>
</tr>
<tr>
<td>Documentation system and specifications available as well as</td>
<td>11 g, 11 j</td>
<td>4.2</td>
<td>6.1</td>
</tr>
<tr>
<td>retention of records</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material controls principles including traceability of material</td>
<td>11 h</td>
<td>7.5.1, 7.5.2, 7.5.3</td>
<td>7.1, 17.2</td>
</tr>
<tr>
<td>Production and packaging operations are under control</td>
<td>-</td>
<td>7.5.1</td>
<td>8.1, 9.1</td>
</tr>
<tr>
<td>Laboratory controls and independent quality control</td>
<td>11 i</td>
<td>8.2.4</td>
<td>11.1</td>
</tr>
<tr>
<td>Contracted operations and written contracts</td>
<td>11 k</td>
<td>7.4.1, 4.1</td>
<td>16</td>
</tr>
<tr>
<td>Complaints are reviewed and products may be recalled</td>
<td>11 l</td>
<td>8.2.1, 8.3</td>
<td>15</td>
</tr>
<tr>
<td>Self-inspection programmes</td>
<td>11 m</td>
<td>8.2.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Any other measures to manage risk (e.g., change control)</td>
<td>11 n</td>
<td>4.3</td>
<td>13</td>
</tr>
<tr>
<td>Specific excipients used in clinical trials</td>
<td>-</td>
<td>-</td>
<td>19.1</td>
</tr>
</tbody>
</table>
A Practical Approach of Implementing GMP for Excipients

Background
In the EU, binding definitions are in place for medicinal products (1) and APIs (2, 3). It is an ongoing process to develop appropriate requirements for pharmaceutical excipients, which represent up to more than 90% of dosage forms.

A series of tragic incidents in the pharmaceutical supply chain caused the European Commission to propose an application of GMP for APIs (3) as guidance for the manufacturing of "potentially" critical excipients in 2007. The assessment report of this public consultation concluded that pharmaceutical companies defining the appropriate GMP for excipients, based on risk, would result in a more pragmatic approach. As a result, the European Commission adapted the legal basis for defining the appropriate GMP for pharmaceutical excipients using a risk-based approach: "The holder of the manufacturing authorisation shall ensure that the excipients are suitable for use in medicinal products by ascertaining the appropriate good manufacturing practice on the basis of a formalised risk assessment" (4). A draft on Guidelines on the Formalised Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practice for Excipients of Medicinal Products for Human Use (5) was submitted for public consultation.

The risk-assessment model proposed and discussed in this article refers to these expectations (5). It also takes into account and provides links to existing guidance developed in the IPEC Europe Excipient Forum.

The recent European Union Falsified Medicine Directive highlights the need for greater public health protection and it is important that all stakeholders contribute towards achieving this goal. The IPEC Europe Excipient Forum has identified the importance of a comprehensive approach to excipient development and manufacture, and continues to work towards developing best practices and guidelines that can be implemented by the industry.

*Patricia Ralphson is global regulatory affairs and compliance manager at Dow Corning, p.ralphson@dowcorning.com. Rinthor Holtz is head of advocacy surveillance Merck Millipore at Merck KGaA, and Stephan Rönninger is head of external affairs Europe, international quality at Amgen (Europe) GmbH.

*To whom all correspondence should be addressed.
• The EU Falsified Medicines Directive requires to apply a risk assessment to ascertain the **appropriate GMP for excipients**
• The new **EU risk assessment guideline** gives **general guidance**
• **Industry** developed a **excipient risk assessment model** to:
  – provide a **simple means** for the excipient user to source and confidently use excipients in their end product
  – help the excipient user recognise and **address the unique hazards** and risks associated with excipients due to them being produced for a wide range of applications
  – encourage excipient manufacturers and users to **work collaboratively to mitigate risk**
  – provide a excipient specific **model that fits with ICH Q9**
Acknowledgements

Thanks to all who supported developing the model

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Thank you