New Classification Guideline

Changes to the Pharmaceutical/Quality part of the Dossier

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Changes to Quality - Overview of presentation

- Key changes
- Impact
- Approach to classification
- New Guideline
- Examples
  - Active substance
  - Finished product
- Future

Key changes

- Type IA – “Tell and Do” to “Do and Tell”
  - Removal of a key barrier
  - Implementation of change (flexibility)
  - Responsibility
- Type IB default (currently Type II)
- Classification Guideline
  - Quality changes covered in current guideline. However, now more comprehensive
  - separate from legislation (facilitation of changes)
- Grouping
- Worksharing
Variations received yearly 1998-2009

Breakdown of variations

UK variations – current breakdown
Approach to the classification guideline

Basic principles
- Based on and complements Annex II of Regulation (list of IA and II variations).
- Based upon current guideline
- Not introducing more stringent requirements than currently
- Look to if possible downgrade some changes
- Need to define Type II changes
- Careful consideration of Type IA/Type IA

Consultation
- Review and update as appropriate

Guideline structure

<table>
<thead>
<tr>
<th>TOPIC / SCOPE OF CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ADMINISTRATIVE CHANGES</td>
</tr>
<tr>
<td>2. QUALITY CHANGES</td>
</tr>
<tr>
<td>a) Active Substance</td>
</tr>
<tr>
<td>b) Control of active substance</td>
</tr>
<tr>
<td>c) Container closure system</td>
</tr>
<tr>
<td>d) Stability</td>
</tr>
<tr>
<td>2. Finished Product</td>
</tr>
<tr>
<td>a) Description and composition</td>
</tr>
<tr>
<td>b) Manufacture</td>
</tr>
<tr>
<td>c) Control of excipients</td>
</tr>
<tr>
<td>d) Control of finished product</td>
</tr>
<tr>
<td>e) Container closure system</td>
</tr>
<tr>
<td>f) Stability</td>
</tr>
<tr>
<td>3. CEP/TSE/monographs</td>
</tr>
<tr>
<td>4. PMF/VAMF</td>
</tr>
<tr>
<td>5. Medical Devices</td>
</tr>
<tr>
<td>III. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES</td>
</tr>
<tr>
<td>1. Human and Veterinary medicinal products</td>
</tr>
<tr>
<td>2. Veterinary medicinal product – specific changes</td>
</tr>
<tr>
<td>Appendix. PMF / VAMF – SPECIFIC CHANGES</td>
</tr>
</tbody>
</table>
Classification Guideline

- **Type IA** – conditions and documentation requirements fully defined (30 days)

- **Type IA - IA/IA_{IN}** – appropriately identified

- **Type II** – changes listed (no documentation requirements) (30, 60, 90 days)

- **Type IB** – **EXAMPLES** with documentation requirements (no conditions) (30 days)

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**Example – finished product manufacturer**

b) **Manufacture**

<table>
<thead>
<tr>
<th></th>
<th>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
<th>Procedure type</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Secondary packaging site</td>
<td>1, 2</td>
<td>1, 2, 3, 8</td>
<td>IA_{EX}</td>
</tr>
<tr>
<td>b)</td>
<td>Primary packaging site</td>
<td>1, 2, 3, 4, 5</td>
<td>1, 2, 3, 4, 8</td>
<td>IA_{IN}</td>
</tr>
<tr>
<td>c)</td>
<td>Site where any manufacturing operations take place, except batch release and secondary packaging, for sterile medicinal products manufactured using a non standard terminal sterilisation method, and biological/immunological medicinal products.</td>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td>d)</td>
<td>Site where any manufacturing operations take place, except batch release, primary and secondary packaging, for non-sterile medicinal products.</td>
<td></td>
<td>1, 2, 3, 4, 6, 7, 8</td>
<td>IB</td>
</tr>
<tr>
<td>e)</td>
<td>Site which requires an inspection</td>
<td></td>
<td></td>
<td>II</td>
</tr>
</tbody>
</table>

**Conditions**:

1. Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.

2. Site appropriately authorised to manufacture the product/active ingredient or product concerned.

3. Product concerned is not a sterile product.

4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.

5. Product concerned is not a biological/immunological medicinal product.
Example – Batch release/QC

<table>
<thead>
<tr>
<th>Change to batch release arrangements and quality control testing of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
<th>Procedure type</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Replacement or addition of a site where batch control/testing takes place</td>
<td>2, 3, 4</td>
<td>1, 2, 5</td>
<td>IA</td>
</tr>
<tr>
<td>b) Replacement or addition of a manufacturer responsible for batch release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Not including batch control/testing</td>
<td>1, 2</td>
<td>1, 2, 3, 4, 5, IAE</td>
<td></td>
</tr>
<tr>
<td>2. Including batch control/testing</td>
<td>1, 2, 3, 4</td>
<td>1, 2, 3, 4, 5</td>
<td>IAE</td>
</tr>
<tr>
<td>3. Including batch control/testing for a biological/immunological product and one of the test methods performed at that site is a biological/immunological/immunochemical method.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conditions:
1. The manufacturer responsible for batch release must be located within the EEA.
2. The site is appropriately authorised.
3. The product is not a biological/immunological medicinal product.
4. Method transfer from the old to the new site or new test laboratory has been successfully completed.

Examples of some changes

Active substance

Finished product

ICH Q8/Q9/Q10 - Design Space
Active substance

Manufacture

Manufacturing site – IA in some instances

Manufacturing process – Minor changes (IA)

Control/test procedures

Addition of a new test parameter – IA

Deletion of obsolete parameter – IA

Active substance

Active Substance Master Files

Manufacturing process – Minor changes to applicant’s part (IA)

Manufacturing process – Minor changes to restricted part (IB)

Annex III Grouping – “All variations in the group are changes to an Active Substance Master File”.
Finished product

Manufacture
Manufacturing site – change for sterile products (IB)
Manufacturing process
- minor change for some dosage forms (IA)
- change to batch size for sterile products (IB)

Control/test procedures
Addition of a new test parameter – IA
Deletion of obsolete parameter – IA

Finished product

Shelf life
Reduction (IA\textsubscript{IN})
Extension (extrapolation) - (IB)

Active substance and finished product
Deletion of sites – multiple deletions as part of the same IA notification
Change to comply with Pharmacopoeia monograph

Active substance – $IA_{in}$

Excipient – IA

ICH Q8/Q9/Q10

Design Space
- Any movement within approved Design Space (No variation)

- Introduction of new or extension of existing Design Space (Type II)

Change Management Protocols
Decision Tree

Specific change

Is it an Extension?

Yes → Extension application

No

Does it meet Type IA (conditions/documentation) requirements?

Yes → \( I_{AI} \) - Immediate notification

No

IA – notification within 12 months

Is it listed as a Type II change?

Yes → Submit as a Type II

No

Submit as a Type IB change?

If listed as an example, address documentation requirements.

Summary

- Changes are very significant – should benefit all

Future

- Something to build on
- System will evolve
- Expectation that the guideline will be regularly updated
  - Experience
  - New recommendations (Article 5)
  - New scientific developments