Variation Regulations (EU)

Headlines of the Update
APIC’s view

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Content

• Scope of regulation:
  Type of procedures and hence 2 strands
• Current status:
  Regulation and guidelines
  When applicable for us?
• Regulation:
  Principles and General provisions
• APIC:
  view and proposal for classification of changes
Content

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**Scope: type of procedures**

- **Initial Marketing Authorisation**
  - 90%
  - 9% Mutual recognition
  - 1% Centr.

- **Variations Regulations**
  - 1004/2003
  - 1990/2003

- **Post-Authorisation Changes**
  - Purely National

- **National rules**
2 strands


Co-decision procedure


Comitology Regulatory Procedure

2 strands (Cont)

• This new Commission Regulation is the comitology part

• In parallel the co-decision part is ongoing to expand the scope of the regulations from currently MRP, CP, DCP to also national submissions


• In March 2008 this proposal was adopted by the EU Commission and send to EU Parliament and EU Council

• Approval by November 2009?
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Current status regulation

• Has been approved by the EU Member States on June 2008
• Has entered into force after a 3 months period of scrutiny by the EU Parliament and the EU Council =13 September 2008.
• No comments from Parliament so publication in October and Official publication in EU journal in November 2008

Current status guidelines

• EU commission coordinates, but EMEA develops
• Kick off: 23 september
  EMEA, CHMP, CVMP, CMS + EU commission
• Draft for industry: 1Q 2009
• Workshop organised by EU commission for industry to comment: 2Q 2009?
When is regulation operational for us?

- Regulation in Nov 2008 with 1 year transitional period->nov 2009
- Supporting Guidelines nov 2009

- Scope broadening to national submissions: start nov 2009 and different timings for implementation per EU country (CMS)

- So 2010-2011?

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Principles

• The actual regulation will no longer contain a classification of variations:
  The classification of the regulations will be in a guideline separate from the regulation.
• Guidelines on the operation of the principles laid down in the guideline will be established.

Principles (cont)

• Variations can be classified in different categories depending on
  – the level of risk to public/animal health and
  – The impact on quality, safety and efficacy of the product
• Changes with highest potential impact require complete scientific assessment, in the same way as for the evaluation of new marketing authorisation applications.
• EMEA and member states should be empowered to give recommendations on the classification of unforeseen variations
Principles (cont)

• To reduce number of variations and to enable competent authorities to focus on variations with genuine impact, an annual reporting system is introduced for certain minor variations. These variations do not require prior approval and should be notified within 12 months following implementation.

• Each variation should require a separate submission. Grouping of variations to several marketing authorisations from the same MA holder only allowed insofar as all concerned MA are affected by the exact same group of variations.

Principles (cont)

• This regulations should clarify when the MAH is allowed to implement a variation.

• Worksharing procedure: 1 authority, chosen amongst the competent authorities of the Member States and the EMEA, should examine the variation on behalf of the other CMS.

• Provisions should be established as regards the role of the coordination groups to increase co-operations between Member States and allow for the settlement of disagreements in the evaluation of certain variations.
General provisions

- Minor variation Type IA: variation which has only a **minimal** impact or **no** impact at all on the quality, safety or efficacy of the medicinal product concerned
- Major variation Type II: variation which is not an extension (see list in annex) and which may have a **significant** impact on the quality, safety or efficacy of the medicinal product concerned
- Minor variation Type IB: variation which is **neither** a minor variation of type Ia **nor** a major variation of type II **nor** an extension.

General provisions (cont)

- Variations which is not an extension and whose classification is undetermined after application of the rules of the Regulation, **by default** are considered minor variation of type IB.
- Or shall be considered a type II in the following cases:
  - Upon request of the MAH
  - If RMS in consultation with CMS (MRP) or the EMEA (CP) conclude upon assessment of the validity of a notification that the variation may have a significant impact on quality, safety or efficacy.
General provisions (cont)

- Prior to submission or examination of a variation whose classification is not provided for in the regulation, a MAH or competent authority may request the coordination group or EMEA (CP) to provide a recommendation on the classification of the variation. (within 45 days following receipt of the request).
- EMEA and the coordination groups shall cooperate to ensure coherence of the recommendations delivered and should publish those recommendations.
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APIC’s view

• Guideline on classification to be developed:
  – Some Industry associations have already
    provided a proposal
  – Industry workshops provide forum for
    discussion with EMEA, member states
  – However, certain topics are specific for API
APIC’s proposal

- A variation which is not an extension and whose classification is not laid down in this guideline shall be considered to be of Type IB.
- A variation which is classified in this guideline as Type IA or Type IAIN but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of Type IB.
- A variation which is classified in this guideline as Type IB but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of Type II.

APIC’s proposal (cont)

|   | Change in the name of the active substance | IA
|---|-------------------------------------------|---
| 3 | Condition: The active substance shall remain the same. |

|   | Change in the name and/or address of a manufacturer of the active substance where no Ph Eur Certificate of Suitability is available | IAIN
|---|----------------------------------------------------------------------------------------------------------------------------------|---
| 4 | Condition: The manufacturing site shall remain the same. |

|   | Deletion of any manufacturing site (including for an active substance where no Ph Eur Certificate of Suitability is available, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place) | IA
|---|----------------------------------------------------------------------------------------------------------------------------------|---
| 9 |                                                                                                                                  |
### APIC’s proposal (cont)

#### 10 (i) Minor change in the manufacturing process of an intermediate in the manufacture of the active substance

**Conditions:**
1. No negative impact on the impurity profile of any one of the following is demonstrated:
   - the intermediate immediately following the modified step
   - any suitable downstream intermediate
   - the active substance
2. The synthetic route remains the same, i.e. intermediates remain the same.

#### 10 (ii) Minor change in the final step of the manufacturing process of the active substance

**Conditions:**
1. No change in the qualitative and quantitative impurity profile or in physico-chemical properties of the active substance, i.e.
   - specified impurities remain within their approved limits
   - no new impurities above the identification threshold are detected
   - residual solvents remain within ICH limits
2. The synthetic route remains the same, i.e. intermediates remain the same.

### APIC’s proposal (cont)

#### 11 Change in batch size of active substance or intermediate

**Conditions:**
1. Any changes to the manufacturing methods are only those necessitated by scale-up, e.g. use of different sized equipment.
2. Test results of at least two batches according to the specifications should be available for the proposed batch size.
3. The change does not affect the reproducibility of the process.
4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
12 (i) Change in the specification of an active substance
   a) Tightening of specification limits  Condition 1  IA
   b) Addition of a new test parameter Condition 2  IA

   Conditions:
   1. Any change should be within the range of currently approved limits.
   2. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

12 (ii) Change in the specification of a starting material / intermediate / reagent used in the manufacturing process of the active substance

   Condition: No change to the specifications of the active substance.

13 (i) Change in test procedure for an active substance
   a) Minor change to an approved test procedure Conditions 1, 2, 3  IA
   b) Other changes to a test procedure, including replacement or addition of a test procedure Conditions 2, 3  IB

   Conditions:
   1. The method of analysis should remain the same (e.g. a change in column length or temperature but not a different type of column or method), no new impurities are detected above the identification threshold.
   2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
   3. Results of method validation show new test procedure to be at least equivalent to the former procedure.

13 (ii) Change in test procedure for a starting material, intermediate or reagent used in the manufacturing process of the active substance

   Condition: New test procedure to be at least equivalent to the former procedure.
### APIC’s proposal (cont)

#### 14 (i) Change in the manufacturer of the active substance where no Ph Eur Certificate of Suitability is available

| a) Change in site of an already approved manufacturer (replacement or addition) | Conditions 1, 2, 4 | IA |
| b) New manufacturer (replacement or addition) | Conditions 1, 2, 4 | IB |

**Conditions:**
1. The specifications (including in-process controls, methods of analysis of all materials), method of preparation and detailed route of synthesis are identical to those already approved or any further modifications fall under Type IA or IB variations.
2. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current Note for Guidance on Minimising Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.
3. The change does not concern a biological medicinal product.
4. Substance in veterinary medicinal product for use in animal species susceptible to TSE

#### 14 (ii) Change in manufacturer of a starting material, intermediate or reagent used in the manufacturing process of the active substance where no Ph Eur Certificate of Suitability is available

**Conditions:** No change to the specifications of the active substance.

### APIC’s proposal (cont)

#### 15 Submission of a new or updated Ph Eur Certificate of Suitability for an active substance or starting material / reagent / intermediate in the manufacturing process of the active substance

| a) From a manufacturer currently approved | Conditions 1, 2a, 2b, 4 | IA |
| b) From a new manufacturer (replacement or addition) | Conditions 1, 2a, 4 | IB |
| c) Substance in veterinary medicinal product for use in animal species susceptible to TSE | Conditions 1, 2a, 2b, 3, 4 | IA |

**Conditions:**
1. The finished product release and end of shelf life specifications remain the same.
2a. Unchanged additional (to Ph Eur) specifications for product specific requirements (e.g. particle size profiles, polymorphic form) if applicable.
2b. Unchanged additional (to Ph Eur) specifications for impurities if applicable, excluding residual solvents when the only change is in compliance with ICH Q3C (in which case Type IA applies). Note – this condition is only intended to apply to situations in which specification limits for new impurities are added.
3. The active substance will be tested immediately prior to use if no retest period is included in the Ph Eur Certificate of Suitability or if data to support a retest period is not provided.
4. The manufacturing process of the active substance, starting material / reagent / intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
## APIC’s proposal (cont)

| 16 | Submission of a new or updated TSE Ph Eur Certificate of Suitability for an active substance or starting material / reagent / intermediate in the manufacturing process of the active substance for a currently approved manufacturer and currently approved manufacturing process | IA |
| 17 | Change in:  
| | a) Retest period of the active substance  
| | b) Storage conditions for the active substance **where no Ph Eur Certificate of Suitability stating the retest period is available.** | IA |
| | **Conditions:**  
| | 1. Stability studies have been done according to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.  
| | 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. | |

## APIC’s proposal (cont)

| 25 | Change to comply with Ph Eur or with the national pharmacopoeia of a Member State  
| | a) Change of specification(s) of a former non-European pharmacopoeial substance to comply with Ph Eur or with the national pharmacopoeia of a Member State  
| | b) Change to comply with an update of the relevant monograph of the Ph Eur or national pharmacopoeia of a Member State | IA |
| | **Conditions:**  
| | 1. The change is exclusively made to comply with the pharmacopoeia.  
| | 2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form) if applicable. | |
## APIC’s proposal (cont)

<table>
<thead>
<tr>
<th>NEW</th>
<th>Change in the packaging of the active substance</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEW</td>
<td>Redefinition of an intermediate as a starting material in the synthesis of the active substance</td>
<td>IB</td>
</tr>
<tr>
<td></td>
<td>Conditions:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. The new starting material is adequately controlled.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. No change to the specifications of the active substance.</td>
<td></td>
</tr>
<tr>
<td>NEW</td>
<td>Change in the manufacturer of the active substance where no Ph Eur Certificate of Suitability is available, which leads to a change in the specifications of the active substance, which is not classified as a Type IA or IB variation.</td>
<td>II</td>
</tr>
<tr>
<td>NEW</td>
<td>Change in the manufacturing process of the active substance involving a change to the route of synthesis or which leads to a change in the specifications of the active substance, which is not classified as a Type IA or IB variation.</td>
<td>II</td>
</tr>
</tbody>
</table>

### Copy of updated regulation available on

Abbreviations

• MA: Marketing authorisation
• MAH: Marketing Authorisation Holder
• CMS: Concerned Member State
• RMS: Reference Member State
• EMEA: European Medicines Agency
• MRP: Mutual Recognition Procedure
• CP: Centralised Procedure