Safety Variations – Implementation Strategies and Experiences

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Safety Variations

- Definitions (EU)
- Safety Signals as triggers for Safety Variations
- Safety Variations at Abbott
- Example
Variations – EU perspective

A variation is a change to the dossier of an authorized product. EU Variation Regulation 1234/2008 describes four types:

• **Type IA variation**: a change that has only a minimal effect, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned (validated, but not assessed)

• **Type IB variation**: a change which is neither a minor variation of type IA change, nor a major variation of type II nor an extension (validated and assessed)

• **Type II variation**: a change which is not an extension and which may have a significant effect on the quality, safety or efficacy of the medicinal product concerned (validated and assessed)

• **Line extension**: a change which is listed in Annex I of the Regulation and fulfills the conditions laid down therein (e.g. change in the active ingredient or a change in the strength or pharmaceutical form)
Type II Variations – EU perspective

• If they concern a single MA, variations may be grouped together, highest ranking defines classification

• several Type II variations to >1 MAs may be grouped together in accordance with the worksharing procedure

• Recommended MoH process timeframes of 30 – 60 – 90 days (‘reduced’ 30 days intended for variations concerning safety issues; ‘extended’ 90 days intended for changed therapeutic indications and complex groupings of variations)
Type II Variations – MRP/DCP procedure

- After validation, RMS completes CTS (European Communication and Tracking System) record to inform the CMS and MAH of the start date (Day 0) – RMS/CMS-agreed timetable is included in CTS

- RMS sends PVAR to MAH and CMSs by the agreed date, clearly indicating whether variation is endorsed, rejected or amended

- Following PVAR receipt, CMS send their opinion to the RMS by the agreed date via MRVE mailbox
**Type II Variations – MRP/DCP procedure**

**Recommended reduced (30-day) procedure for type II variations**

<table>
<thead>
<tr>
<th>Day</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email</td>
</tr>
<tr>
<td>15</td>
<td>RMS circulates the PVAR to the CMS's and to the MAH</td>
</tr>
<tr>
<td>20</td>
<td>CMS's send the possible comments on the PVAR to the RMS</td>
</tr>
</tbody>
</table>
| 21   | RMS sends the request for supplementary information to the MAH and the CMS's, clock stop  
      | Should not be longer than 10 + 10 days (10 days for the MAH to provide the responses and 10 days for the RMS to prepare the FVAR) |
| Clock off period |  |
| 22   | RMS circulates the FVAR to the CMS's and to the MAH |
| 27   | CMS's send the possible comments on the FVAR to the RMS |
| 30   | End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH |
### Type II Variations – MRP/DCP procedure

**60-day procedure for type II variations**

<table>
<thead>
<tr>
<th>Day</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email</td>
</tr>
<tr>
<td>40</td>
<td>RMS circulates the PVAR to the CMS’s and to the MAH</td>
</tr>
<tr>
<td>55</td>
<td>CMS's send the possible comments on the PVAR to the RMS</td>
</tr>
<tr>
<td>59</td>
<td>RMS sends the request for supplementary information to the MAH and the CMS’s, clock stop</td>
</tr>
<tr>
<td></td>
<td>Should not be longer than 60 + 60 days (60 days for the MAH to provide the responses and 60 days for the RMS to prepare the FVAR)</td>
</tr>
<tr>
<td>60</td>
<td>RMS circulates the FVAR to the CMS's and to the MAH</td>
</tr>
<tr>
<td>75</td>
<td>The possible break-out meeting</td>
</tr>
<tr>
<td>85</td>
<td>CMS's send the possible comments on the FVAR to the RMS</td>
</tr>
<tr>
<td>90</td>
<td>End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH</td>
</tr>
</tbody>
</table>
## Type II Variations – MRP/DCP procedure

### 90-day procedure for type II variations

<table>
<thead>
<tr>
<th>Day</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Start of the procedure. RMS notifies the timetable to the CMS's by CTS and to the MAH by email</td>
</tr>
<tr>
<td>70</td>
<td>RMS circulates the PVAR to the CMS's and to the MAH</td>
</tr>
<tr>
<td>85</td>
<td>CMS's send the possible comments on the PVAR to the RMS</td>
</tr>
<tr>
<td>89</td>
<td>RMS sends the request for supplementary information to the MAH and the CMS's, clock stop</td>
</tr>
<tr>
<td></td>
<td>Should not be longer than 90 + 60 days (90 days for the MAH to provide the responses and 60 days for the RMS to prepare the FVAR)</td>
</tr>
<tr>
<td>90</td>
<td>Re-start of the procedure. RMS circulates the FVAR to the CMSs and to the MAH</td>
</tr>
<tr>
<td>105</td>
<td>The possible break-out meeting</td>
</tr>
<tr>
<td>115</td>
<td>CMS's send the possible comments on the FVAR to the RMS</td>
</tr>
<tr>
<td>120</td>
<td>End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH</td>
</tr>
</tbody>
</table>

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Type II Variations – referrals (national procedures)

Safety signal triggers an Art. 30 or 31(1) referral with complete harmonisation as outcome (rare event)

purely national MAs have to be transferred into MRP status.

Implementation of Commission Decision into national translations to be submitted as a type IA variation according to classification guideline category C.l.1.a.

"Recommendation for Mutual Recognition Procedure after Finalisation of a Referral Procedure with a Positive Decision by the Commission" (CMDh/101/2001).
Type II Variations – referrals (national procedures)

e.g. Germany

For the implementation of the Commission decision (CD) in purely national MAs concerning a referral Art 31(2) it is the obligation of the MAH to follow the requirements of § 29 Arzneimittelgesetz (= AMG; German Medicinal Products Act) and to submit a national variation application.

For products not included in the Commission decision it is highly recommended to adapt to the Commission decision. Depending on the route of marketing authorisation (only national or MRP/DCP) this can either be done with a national variation according to § 29 AMG or with a Type IB notification according to category C.I.1.b (within 90 days after CD).
Type II Variations – national procedure

Processes and timelines vary broadly between countries

e.g. Germany

• MoH validation timeframe for Type II Variations usually is 14 days

• Variations concerning pharmaceutical quality cannot be combined with variations concerning efficacy, safety and PV, unless they are clearly interdependent

• Variations of purely national procedures may be combined in a worksharing procedure with other countries‘ national procedures or MRP/DCP or CP

• For Type II Variations, in case of deficiencies a catalogue of questions will be provided (‘Request for Supplementary Information‘); clock stop no longer than 60 days
Type II Variations – national procedure

e.g. Ukraine

4.4.2. In case of introduction of major Type II changes the application may apply to only one Type II change. If several Type II changes are necessary to be introduced, then separate (individual) applications shall be submitted for every change; every such application shall refer to the other application(s).

If Type II change causes other successive Type II changes one application may include all successive changes together with a description of correlations between these successive Type II changes.

Attached to the application should be: materials which substantiate the introduction of changes; relevant materials with amendments made in accordance with the application; amended or updated existing expert reports (reviews, conclusions) taking into account the changes.
Type II Variations – national procedure

e.g. Ukraine

4.2.2. … In case the Applicant becomes informed about the revealed unsafe properties of the medicinal product for human health or life which are a reason for him
to take a decision on restrictions of its medicinal use,

the Applicant shall inform the Center in any way and submit the application for variations associated with the revealed safety problems supported by the appropriate documentation immediately, and in any case

within 15 days after the receipt of this information.
Sources of Safety Variations

Safety Variations most often are due to

safety signals
Sources of safety signals

- Medical review of *Individual Case Safety Reports* (ICSRs)
- Screening of literature and social media
- Preparation of periodic safety reports and aggregate data review
- Inquiries from HCP, consumers or otherexternals
- Communication with regulatory authorities
- Information with potential safety impact re product quality
Safety signals require

• validation,

• prioritization,

• assessment;

• initiation of corresponding action, and

• communication – internal and external
safety signals - validation

Does the available documentation suggest a new potentially causal association, or a new aspect of a known association?

Is it strong enough to justify further assessment of the signal?

- Aim is to separate “noise” from “true” signals.
- Signal validation and prioritization must be completed within 30 days after detection.
- Safety signals notified by regulatory authorities are always validated.
safety signals - prioritization

• Review the data for plausibility, quality, strength of evidence, frequency of harm, and potential impact on individual and public health.

• Prioritize every validated signal by setting a deadline for assessment.

All validated signals are assessed within 60 days after detection.
To assess the level of certainty regarding a causal association between the event and the product in question

To assess the implications of a confirmed signal for public health and the benefit-risk profile of the product, and

To recommend actions suitable to mitigate patient risk and optimize the benefit-risk profile of the product.

→ safety variations
safety signals – assessment

Outcome of confirmed signals, i.e. a recommendation for action(s) - agreed with Product Safety Team; e.g.:

• Heightened surveillance
• Transferal to Labeling Subteam/Regulatory Affairs for possible label change
• Initiation of RMP preparation or update
• Escalation to Senior Safety Committee
Safety Variations – *the process*
Safety Variations – *the process*

- drugs with a **well-established safety profile**
- change in the approved label as most frequently recommended risk minimization strategy
- signal assessment report complemented by a *Clinical Overview Addendum* document with a proposal for a safety variation
Safety Variations – the process

Signal Validation and Assessment Report

Clinical Overview – Addendum*

Proposed New Label

EPD Global Labeling Committee

GPV – Medical Safety Expert or Product Safety Team

Labeling Subteam

Affiliate

Authority(ies)

*not for alignment with originator and other reference documents
Safety Variations – the process

- standard timing of safety variation process
- regulated individually per company
  - criticality assessment
  - metrics system tracking
- authority submission of an approved signal for label change is expected in due time, e.g. +/- 6 months after signal approval
Safety Variations – strategies

- **Grouping of variations** in order to avoid increased administrative burden and costs

- **Global departments** prepare documentation (signal assessment reports, clinical overviews, medical expert statements)

- Country specific safety variations are discussed within **global multidisciplinary teams** (e.g. labeling subteam)

- Timeline deviations require **upper management** approval (e.g. EPD Global Labeling Committee)
Midazolam

Drug A is a well-documented substrate and inhibitor of CYP3A. Many of the drug interactions associated with drug A are attributed to its effects on CYP3A activity. Certain benzodiazepines, including midazolam, are primarily metabolized by CYP3A. When midazolam was co-administered with drug A, the midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration.

An update to the existing statement in the Special Warnings and Precautions for Use section was made to the CCDS and is proposed for the SmPC to clarify that during concomitant administration of intravenous midazolam with drug A, the patient must be closely monitored to allow dose adjustment while the concomitant administration with oral midazolam should be avoided and is now presented as a contraindication.
Ergot alkaloids

The known pharmacokinetic properties of drug A and ergot-containing preparations via the CYP 3A4 enzyme pathway pose a risk for acute ergot toxicity when co-administered. Specific updates to include a contraindication for concomitant administration with ‘ergotamine’ and ‘dihydroergotamine’ were made to the CCDS in 2004 and subsequently incorporated into SmPCs. In the February 2013 CCDS update, revisions to the Contraindications and Interaction with Other Medicinal Products and Other Forms of Interactions section were made to clarify the contraindication applies to the class of ergot alkaloids.
Safety variations - Example

The event of interest “mania” was detected during routine literature research. In a literature article a report of drug A-associated mania in a patient with a history of medically treated depression was described. The literature research conducted showed that manic reactions are infrequently described with drugs of the same class.

Mania is characterized by euphoria or irritability, increased psychomotor activity, distractibility, and poor judgment. It usually occurs in bipolar disorder and is a state of abnormally elevated or irritable mood, arousal, and/or energy levels. Mania is a criterion for certain psychiatric diagnoses such as bipolar or schizoaffective disorders.

Of 126 ICSR reports, 34 reports could not show an alternative etiology for the development of mania. In 20 of these, the manic behavior subsided after discontinuation of drug A and corrective treatment with antipsychotic medication, whereas in 14 reports the manic symptoms subsided upon discontinuation of drug A without any further drug treatment. One of these patients also had a positive rechallenge.

In summary, mania has been reported with drug A and drugs of the same class. A relationship cannot be excluded and an update of the reference safety information is thus recommended.
Safety variations - Example

- **One** Clinical Overview Addendum report was prepared
- This incorporated all information from **two administrative processes** (Midazolam and Ergot Alkaloids) and **one signal assessment** (Mania)
- **Thus procedural efforts and costs were reduced**
- Due to the **modular nature** of the single documents, and the broad coverage **layout of the COA**, repeat-use is possible
- Further, **country-specific procedures** (e.g. CMC, administrative) could be added as well
Questions ?