New Variations Regulation 6 months experience

Sonia Ribeiro
1-2 June 2010, London, UK
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
Agenda

- Aim of new Variations Regulation
- Main features & scope
- Experience with new provisions
- Points for discussion
Aim of New Regulation

- Simpler, Clearer, More flexible legal framework
- Reduce administrative burden
- Adapt to ICH concepts
- Further harmonise handling of variations in EU

Same level of public and animal health protection
Main Features & Scope

- Type IA ‘Do and tell’ *(annual reporting)*
- Type IB by default & Article 5
- Grouping *(facilitate review & reduce administrative burden)*
- Worksharing *(avoid duplication of work)*
- CMD referrals *(increase cooperation between MSs)*
- Implementation of variations by MAH
Main Features & Scope

- Classification of variations depending on **level of risk** to public or animal health &
- **Impact** on the quality, safety and efficacy of medicinal product concerned

- **Applies to:**
  - Medicinal products authorised via **MRP, DCP**
  - Following a **CHMP referral** (full harmonisation)
  - Medicinal products authorised via **CP**
Types of Variations

Changes not requiring prior approval

Design space

Type IA

Type IB

Changes requiring prior approval

Type II

Extension

Do and tell

Variations

Evaluation Procedure adapted to the level of risk
Submission of Variations

~ 22% Submissions in 2010 grouped
Type IA notifications

- Variation which has minimal impact or no impact on the quality, safety or efficacy

\[ \text{IA}: \text{Agency notified within 12 months following implementation} \]

\[ \text{IA}_{\text{IN}}: \text{Agency notified immediately* after implementation} \]

*Changes for which continuous supervision is needed*
**Implementation**

- Quality change - change in the Company’s quality system*
- PhV change - when Company makes the change in the DDPS
- Product information (PI) - when revised PI is approved

* This allows Companies to manufacture conformance batches and generate data necessary before immediate notification
Type IA notifications

Submission of Type IA notifications, T1 2010

- IG: 3%
- IA (IN): 34%
- IA: 27%
- IA grouped: 36%

Total submissions: 168
Type IA notifications

Submission of Type IA notifications T1, 2010

- A1: 29%
- A2: 4%
- A4: 4%
- B.I: 5%
- B.II: 1%
- B.II: 3%
- B.III: 6%
- B.IV: 5%
- C.I: 37%
• Number of submissions for Type IA in 2010 ≈ 2009 (256 vs 253)
• Total number of notifications increased in 2010 by ~ 60%
• IG notifications contain an average of 5.6 products
• Examples of IG notifications:
  ➢ A.7, B.II.d.1.c, B.III.1.a.2, C.I.9
Type IA notifications

• MAHs advised to submit Type IA variations as part of the **Annual Report**, except for:
  - Type IA$_{IN}$ – To be submitted immediately!
  - Type IA affecting the PI - To be submitted with the next variation affecting the PI

➤ Further reduce overall number of variations submissions
➤ Better use of Competent Authorities resources
Type IA notifications

• Possible to group, Art. 7.2(a):
  >1 type IA or IA_{IN} affecting one MA
  1 type IA or IA_{IN} affecting >1 MA
  >1 same type IA and/or IA_{IN} affecting >1 MA

- All Type IAs listed in the guideline
- Quality or S/E, PhV changes
- Conditions to fulfil & documentation to be provided
Type IB notifications

- Number of submissions in 2010, 20% > in 2009 (141 vs 169)
- Total number of notifications increased in 2010 by ~25%
- Number of Type II variations 30 days ≅ Type IB notifications C.I
- ~ 16% Type IB ‘unforeseen’
Unforeseen Variations

- Not listed in the classification guideline
- Not classified as Type IB via Article 5 recommendation
- Justification for proposed classification in the application form

Note: If a condition for a Type IA is not met NOT unforeseen but ‘default’ Type IB
<table>
<thead>
<tr>
<th><strong>Art 5</strong></th>
<th><strong>Art 3(2) &amp; 3(3)(b)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification within 45 days</td>
<td>‘Reclassification’ during validation (approx. 2 wks)</td>
</tr>
<tr>
<td>EMA, CMD, WPs, EC</td>
<td>EMA/MS only</td>
</tr>
<tr>
<td>Publication of each recommendation</td>
<td>No publication</td>
</tr>
<tr>
<td>Basis for other similar variations for CAPs/NAPs and update of the guideline</td>
<td>Basis for the update of the guideline</td>
</tr>
</tbody>
</table>
Practical Experience

- No requests to the Agency for Article 5 recommendations!

**Why?**
- Request for advice from PTL/PTM before submission?
- Submission as Type II variation?
- Duration of procedure 45 days?
- Outcome binding?

- Agency involved in requests for Article 5 recommendations to CMDs
Type II variations

Submission of Type II variations T1, 2010

- B.I: 65%
- B.II: 22%
- B.IV: 13%
- C.I: 0%

Reduced by ~27% compared to the same period in 2009
Cases of acceptable grouping listed in Annex III or agree with the Agency before submission.

Grouping should always be justified & meaningful to be reviewed simultaneously.

Quality, Non-clinical & Clinical cannot be grouped, unless justified.

Quality variations to active substance cannot be grouped with finished product, unless justified.

Grouping should *not delay the submission and implementation of safety information*.
Set up of G-WAG (Grouping and Worksharing Advisory Group)

- To advise on acceptability of proposed groupings and/or worksharings
- To ensure a consistent approach within the Agency and provide internal support to PTLs
- To keep track of accepted groupings and/or worksharings and to publish this information
- Agency staff with scientific & regulatory experience (human or veterinary)
- ~ 50 requests on grouping
Practical Experience

- Consider carefully groupings proposed, i.e.:
  - Facilitate review of variations?

- Avoid ‘super’groupings (e.g. extension + new indication + quality changes to active substance and finished product)

- If Type IA not directly related or consequential - Annual report

- No need to consult the Agency for groupings of Type IA notifications only!
Worksharing

Same change(s) applying to different MAs

• **Same dataset**; no need for product specific assessment => Worksharing **OK**

• **Common dataset**, but with limited need to review impact on individual products => Worksharing **OK**

• **Separate datasets** for each individual product which require separate assessments => **NO** Worksharing
Worksharing

- Worksharing includes an average of 3 products
- Only 1/21 worksharing including MRP products
- Duplicates routinely accepted for worksharing
- ~ 38 requests on worksharing
- Examples of worksharings:
  - B.II.b.1, C.I.2, C.I.3
Worksharing

Submission of Worksharing per procedure type, T1, 2010

- IB grouped: 10%
- IB: 38%
- II: 47%
- II grouped: 5%
Points for discussion

• Positive aspects:
  ✓ Principles for classification of variations
  ✓ Downgrading of Variations
  ✓ Implementation of Variations
  ✓ Classification guideline for individual changes
  ✓ Type IA ‘Do and Tell’ & Annual report
  ✓ Type IB by default
  ✓ Worksharing
Points for discussion

• **What needs to be improved?**
  - Need to simplify submission & handling of multiple changes/groupings?
  - Classification guideline & application form not optimal for multiple changes/grouping?
  - Increase submission of Type IA notifications as part of Annual Report!
  - Others?
Conclusion

• The Agency is committed to contribute to achieve aim of new Variations Regulation
• Continue to participate in CMD Variation Sub-group
• Ensure a harmonised approach with MSs on classification of variations, Article 5 recommendations, grouping and worksharing
• Contribute to the revision of the classification & procedural guidelines
Thank you very much!

Any questions?

Sonia Ribeiro
Regulatory Affairs Adviser
+44(0)20 7523 7231
sonia.ribeiro@ema.europa.eu