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Practical Advice on Submission of Variation Applications

Information Day on the New Variations Regulation, 22nd Jan 2010

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Introduction

- IMB Application of the Regulation
- Type IA/IB/II Variations
  - Focus on “purely national” products
- Grouping & Worksharing

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Regulation 1234/2008

- Applies from 1st Jan 2010 to all products authorised through centralised procedure, MRP and DCP.

- IMB Policy: To implement the *principles* of the Regulation to nationally authorised products.

  Key exceptions:

  - Timelines not yet applicable for type IB/II
  - "Automatic approval" of IB not applicable

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General Comments

- Documentation requirements previously discussed.
- Electronic submissions (RIO/eCTD/non-eCTD) strongly encouraged.

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Type IA Notifications

- "Do and tell"
- Notification accepted via:
  - Standalone application
  - Grouped submission
  - Annual report
- Primarily an "Administrative check"
- No correspondence, clarification or clock-stops

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Type IA_{IN} Notifications

- Notification accepted via:
  - Standalone application
  - Grouped submission

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Implementation of IA Changes

- Definition of “Implementation”
  - Case-by-case situations
  - General Rule: When change is approved internally by manufacturer/MAH
  - Product information: When change is signed off, not when released to market
- Inspections

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Unacceptable IA Notifications - 1

- ONUS IS ON APPLICANT
- Ongoing monitoring of quality of submissions.
- IMB reserves right to subsequently reject IA notifications.
- Non-compliance with conditions and/or documentation requirements.

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Unacceptable IA Notifications- 2

- Implementation must cease
- Remedial Action?
  - Refer to Market Compliance section
  - Batch-Specific Request may be required
  - Recalls/Caution-in-Use Notification

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Type IA/IA_{IN} – Miscellaneous

- Submission of mock-ups still required where applicable
  - Only changes directly applicable to relevant IA
- Changes to product information must be clearly indicated.
- NB: Notification to healthcare professionals/patients

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Notification to HCPs/Public - Examples

Change Category	Description
B.II.a.2	Change in shape/dimensions of pharmaceutical form
B.II.a.3 (a)	Changes in components of the flavouring or colouring system
B.II.e.6	Change in any part of packaging… e.g. colour of flip-off caps, colour code rings on ampoules, change of needle shield

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Type IB Variations

- "Default category"; list in Classification Guideline is not exhaustive
- National Authorisations – Concept of "automatic approval" after 30 days not applicable.
- One RSI/Clock-stop Period

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Type II Variations

- Procedures largely unchanged
- No longer “default” category
- Maximum of two clock-stops

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“Unforeseen Variations” - 1

1. Classification guideline
   - Listed as IA but condition not met = IB
2. Annex II of 1234/2008
3. Published Article 5 recommendations

NB:

Application Form: Requires justification of classification

Proposed classification subject to review by IMB

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“Unforeseen Variations” - 2

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product			Procedure type		
☐	a)	Up to 10-fold compared to the currently approved batch size	☐IA	☐IB[9]	**Implement. Date:**
☐	b)	Downscaling down to 10-fold	☐IA	☐IB[9]	**Implement. Date:**
☐	c)	The change requires assessment of the comparability of a biological/immunological medicinal product.	II		
☐	d)	The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	II		
☐	e)	More than 10-fold increase compared to the currently approved batch size for immediate release	IB		
☐	f)	The scale for a biological/immunological medicinal product is increased / decreased without process change (e.g. duplication of line).	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

[9] If one of the conditions is not met and the change is not specifically listed as Type II.

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Grouped Variations - 1

- If type IB and/or type II involved – only a single MA may be included in the group
  - Ref: Definition of “single MA”
- All changes follow longest timeline
- “Do and tell” still applies except where IA is directly consequential to IB/II

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Grouped Variations - 2

- Single application form
- All supporting documents
  - Changes to product info may be combined
- Justification for grouping required

  Ref: Annex III of 1234/2008

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Worksharing

- Currently not possible for nationally authorised products.
- Centralised & MRP/DCP procedures as per EMEA/CMD guidance.

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Closing Remarks

- Queries Raised & Early Experience of Applications
- Q&A on www.imb.ie

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