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EC Procedural Guideline & Summary of the Main Procedural Changes

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

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Overview of Presentation

- Introduction to the new Variations Regulation
- Application of the new Variations Regulation and associated Guidelines at a national level
- Outline of the main aspects of the Procedural Guideline with a focus on purely nationally authorised products

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Regulation (EC) No 1234/2008

- Review of the existing regulation initiated under ECs 'Better Regulation' initiative
- Agreed on 10th Jun 2008 & published on 24th Nov 2008
- Applies fully to products authorised via the centralised procedure or MRP/DCP from 1st Jan 2010

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Directive 2009/53/EC

- Published on 18th June 2009 and applies from 20th Jan 2011
- Will allow the Variations Regulation to be applied to purely nationally authorised products

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Application of New Variations Regulation and Associated Guidelines in Ireland

- IMB has taken a policy decision to apply the principles of the new regulation to all nationally authorised products from 1st Jan 2010. Timelines and automatic approval procedure for Type IBs do not currently apply to nationally authorised products but will apply at a later date.

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Development of Procedural Guideline

- Art 4 of Regulation states that EC should draft a Procedural and Classification Guideline
- EC asked the Variations Taskforce and EMA/CMD Variations Subgroup to develop a draft Procedural Guideline, which was published on EC website for public consultation
- Final official version of Guideline published on EC website in Dec 2009

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Categories of Variations

- Type IA (IA and IA_{IN})
- Type IB
- Type II
- Extensions
- Urgent safety restrictions

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Layout of Procedural Guideline

- Gives details of the procedures and the documentation to be submitted for each type of variation
- Two sub-sections:

  a) National procedure

  b) Centralised procedure

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Type IA Variations

- Do not require prior approval - “do and tell”

- Exception: where a Type IA change is directly linked to a more substantial change (e.g. Type IB or II) that requires prior approval, grouping should be considered and the Type IA change should be implemented after the approval of the group

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Submission of Type IAs

- 2 Subcategories (defined in classification guideline)

  (1) Notify immediately – IA_{IN}

  (2) Notify within 12 months of the implementation of the change – IA

  - commonly being referred to as 'Annual Report'

- There is no specific procedure for an 'Annual Report' – It is a single or grouped Type IA variation.

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‘Annual Report’

- May not be necessary to submit a so-called ‘Annual Report’:
  a) Can group Type IAs with other relevant variations if conditions for grouping met
  b) Might not implement any Type IA changes within a 12 month period

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Type IA – Documentation to be submitted

- Cover letter
- Completed Application form
  - Details of MAs concerned
  - Description of variations submitted
  - Date of implementation
- Copy of the relevant page(s) from the Classification guideline indicating that all conditions and documentation requirements are met or a copy of the relevant published Art 5 recommendation

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Type IA Documentation to be Submitted (2)

- Documentation specified in the Classification Guideline
- Revised SmPC, labels and/or package leaflet, if relevant
- For grouped variations concerning several MAs from the same MAH:

  - Common cover letter and application form

  - Separate supportive documentation and revised product information (if applicable) for each medicinal product concerned.

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Processing of Type IAs

- 30 day review period following receipt
- If accepted MA to be updated:

  - Within 2 months of acceptance for IA

  - Within 6 months of acceptance for IA_{IN}
- If unacceptable MAH will be requested to take appropriate corrective action.

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Type IB Variations

- New regulation expected to lead to increased numbers of Type IBs
  - ‘Default category’ – can be used for ‘unforeseen variations’
  - Downgrading of existing Type IIs
- Examples of changes that would be considered appropriately classified as Type IBs are given in the classification guideline.

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Type IB Variations - Documentation

Similar to that for a Type IA apart from:

- No requirement to state the date of implementation in the application form
- Where a variation is considered unclassified, a justification for its submission as a Type IB should be included in the application form
- No conditions in Classification Guideline
- For variations requested by a competent authority (CA) resulting from new data submitted (e.g. pursuant to post-authorisation conditions), a copy of the request should be annexed to the cover letter

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Type IB Validation

- During validation if the CA does not agree with the classification of an ‘unforeseen variation’ as a Type IB, the MAH will be requested to upgrade the variation to a Type II.

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Type IB Review Process

- Once validated procedure unchanged
  30 (+30) day timetable
- One round of correspondence allowed. If applicant does not respond within 30 days application can be rejected
- If CA has not send the applicant an unfavourable opinion within 30 days of validation, the change is automatically deemed to be accepted – **N.B. Does not apply immediately to purely nationally authorised products in Ireland.**
- Change can be implemented immediately after approval. Updated MA to be issued within 6 months.

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Type II Variations - Documentation

- Documentation to be submitted is similar to that for Type IA apart from the following:

  - No requirement to state the date of implementation in the application form

  - No conditions. Classification guideline only includes documentation for variations related to design space

  - Update/Addendum to expert reports as relevant

  - For variations previously requested by a CA, a copy of the request should be annexed to the cover letter

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Review of Type II Variations

- 60 day default timetable, 30 day for urgent, 90 days for change/new indication
- Change can be implemented 30 days after approval
- Implementation time for safety issues to be agreed between CA and applicant
- Updated MA to be issued within 2 months of approval or within 30 days if the variation results in an extended data protection period

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Other Application Types Addressed in the Procedural Guideline

Extension

- Procedure unchanged
- 210 day default timetable

Human Influenza Vaccines (Annual Update and Pandemic)

Urgent Safety Restrictions

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Grouping

- Can only group variations from the same MAH
- Level of grouping allowed depends on the types of changes included in the proposed group
- Single cover letter and application form (+ extension form if applicable)
- Simultaneous review according to the normal timeline for the most significant element of the group

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Grouping – Definition of the Same MAH (1)

- Grouping can only be done by a single MAH as defined in the introduction to the procedural guideline.

  Includes applicants belonging to the same mother company or a group of companies and applicants having concluded agreements or exercising concerted practices concerning the placement on the market of the relevant medicinal product.

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Grouping – Definition of the Same MAH (2)

- When submitting grouped applications, applicants are encouraged to provide an explanation on the link between the MAHs

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Grouping – Definition of a MA

- For the purposes of grouping it has been agreed that a MA can be considered to consist of all strengths and pharmaceutical forms of a given product – this does not affect the national definition of a MA.

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Grouping of Variations for 'Purely' National Products and Products in MRP

- At present it is not possible to group variations for purely nationally authorised products and products in MRP.
- Not possible to group variations for products in CP and products in MRP / purely nationally authorised products.

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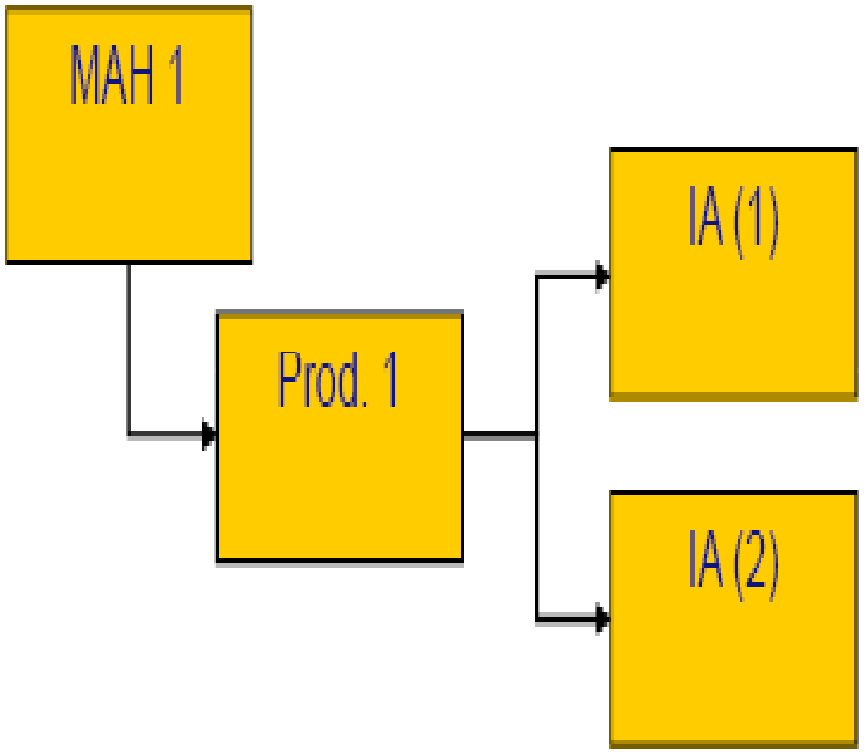
Grouping of Type IA Variations (1)

- More than one Type IA or IA_{IN} affecting one MA



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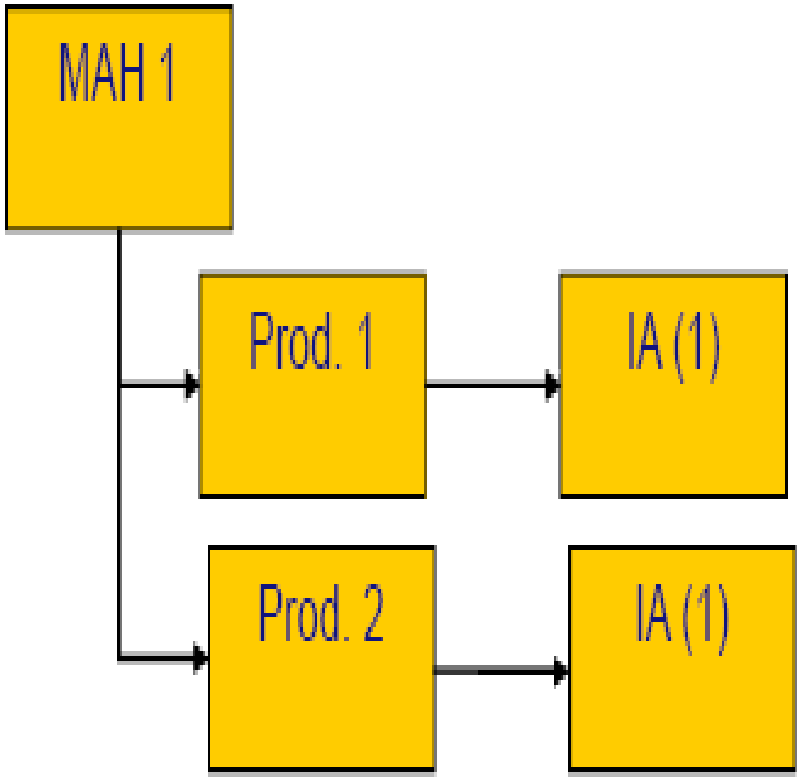
Grouping of Type IA Variations (2)

- One Type IA or IA_{IN} affecting more than one MA from the same MAH provided that the same changes apply to all MAs in group



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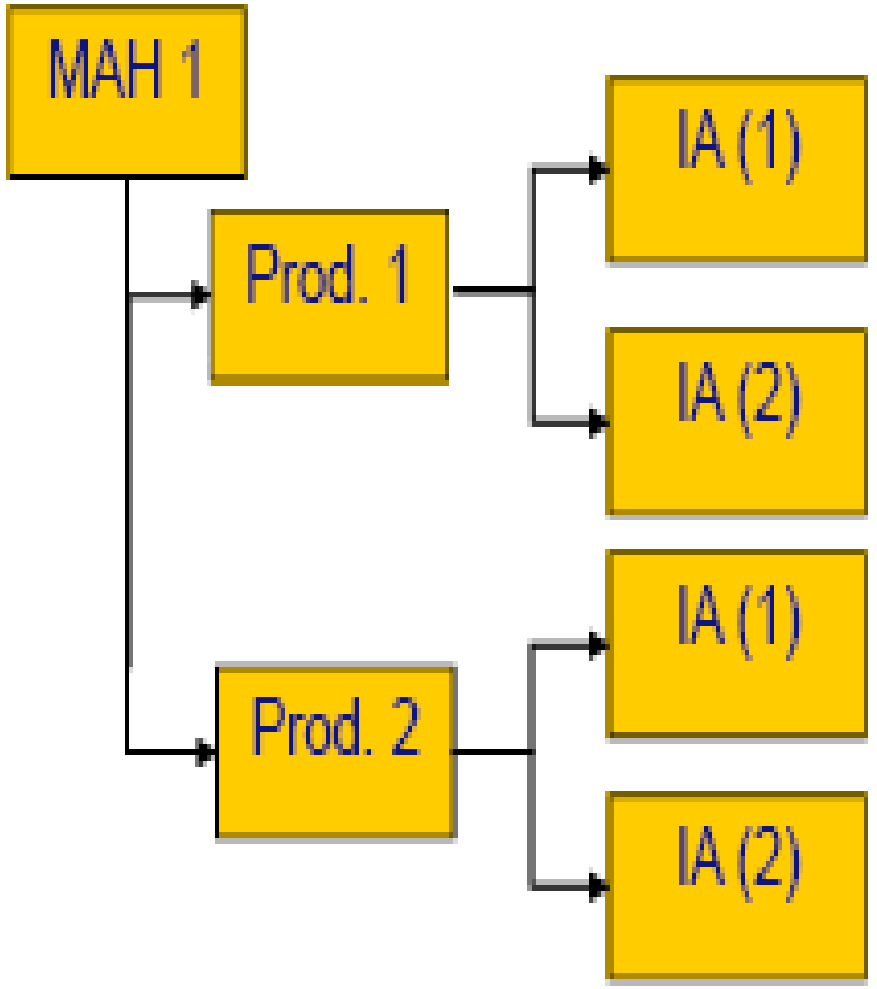
Grouping of Type IA Variations (3)

- Several Type IAs for multiple MAs held by the same MAH provided that the same changes apply to all MAs in group
- Standard Type IA timetable will apply in these cases



Grouping of Multiple Application Types (1)

- Can group several Type IA, IB, II variations or line extensions for the same MA, if the proposed group is in line with one of the cases for grouping listed in Annex III of the Regulation
- It is also possible to apply grouping in other cases if agreed with the CA – MAHs should contact the CA at least two months in advance of the proposed submission date.

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Grouping of Multiple Application Types (2)

Grouping should be justified:

- Changes should be related and suitable for simultaneous review
- Grouping across separate Modules of the dossier (e.g. quality and clinical) not likely to be accepted unless justified
- Quality variations to the active substance should not be mixed with finished product variations, unless justified
- Grouping should not delay updates to safety information

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Grouping of Multiple Application Types (3)

- Examples of acceptable / non-acceptable grouping will be published by CMD.
- The grouped variation will follow the same procedure as the most significant variation in the proposed group, e.g. if group consists of Type IAs, IBs and IIs, the Type II procedure will apply.

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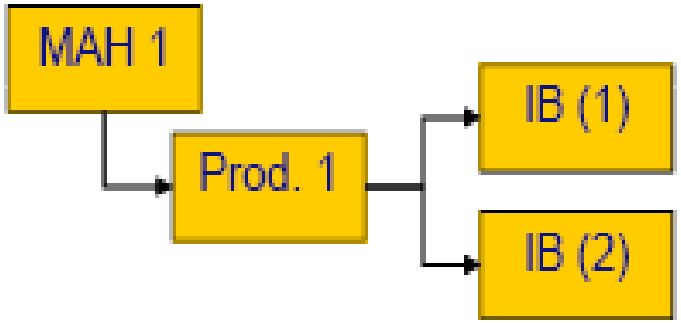
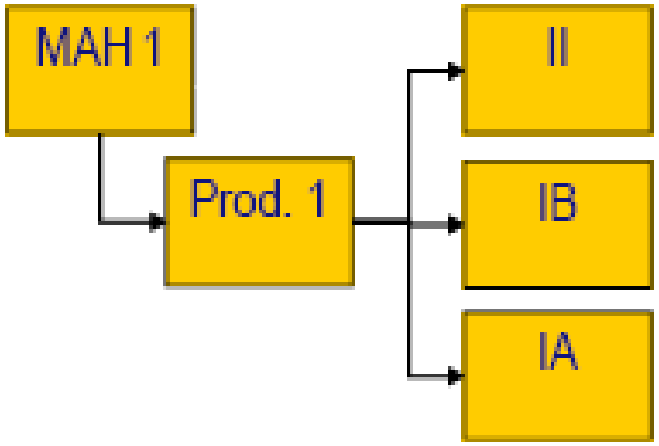
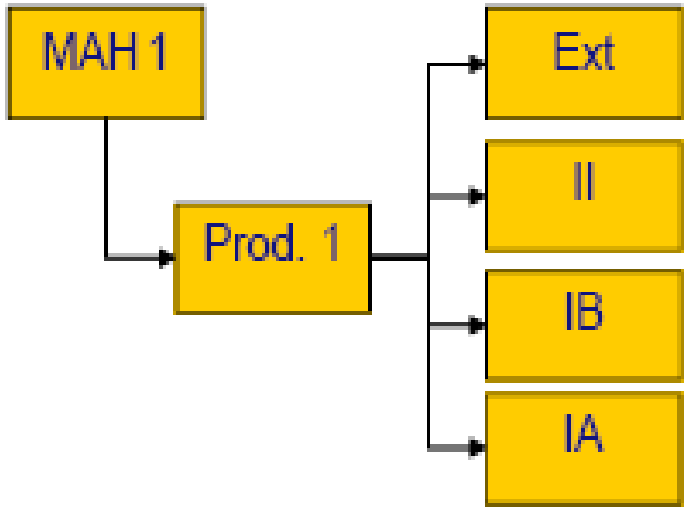
Grouping of Multiple Application Types (4)







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Outcome of Grouped Variations

- Approval, refusal/withdrawal, partial approval
- If individual changes in a group are withdrawn by the applicant or deemed non-approvable following assessment, a letter clearly stating which changes have been approved and which changes have been refused or withdrawn will be issued by the CA.

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Application Form and User Guide

- Application form has been published on the EC website
- Explanatory notes (user guide) to give guidance on the completion of the application form have also been published on the CMD(h) website

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Conclusion

- New regulation includes important procedural changes which should help to streamline procedures and lead to more efficient processing of variations.
- Links to all documents mentioned in this presentation have been published on the IMB website.
- Further guidance (e.g. Q&As) will be published on the IMB website as more experience gained.

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