IRISH MEDICINES BOARD

The EC Classification Guideline

IMB New Variations Regulation Information Day 2010

Mary O'Grady
Quality Assessment Manager
Irish Medicines Board

The EC Classification Guideline

- Background
- Types of Variations
- Classifications
- Some Examples
- Impact

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Background

- **Variation** – amendment to the contents of a MA dossier
- **Handling of variations** requires significant administrative and regulatory resources
- In 2006, EC announced its intention to make the variation regulations **simpler, clearer and more flexible**
- **Aim**: reduction of administrative burden to industry, simplification of the procedures (Better regulation)
- **One regulation** 1234/2008 not two (ex-1084/2003 & 1085/2003)

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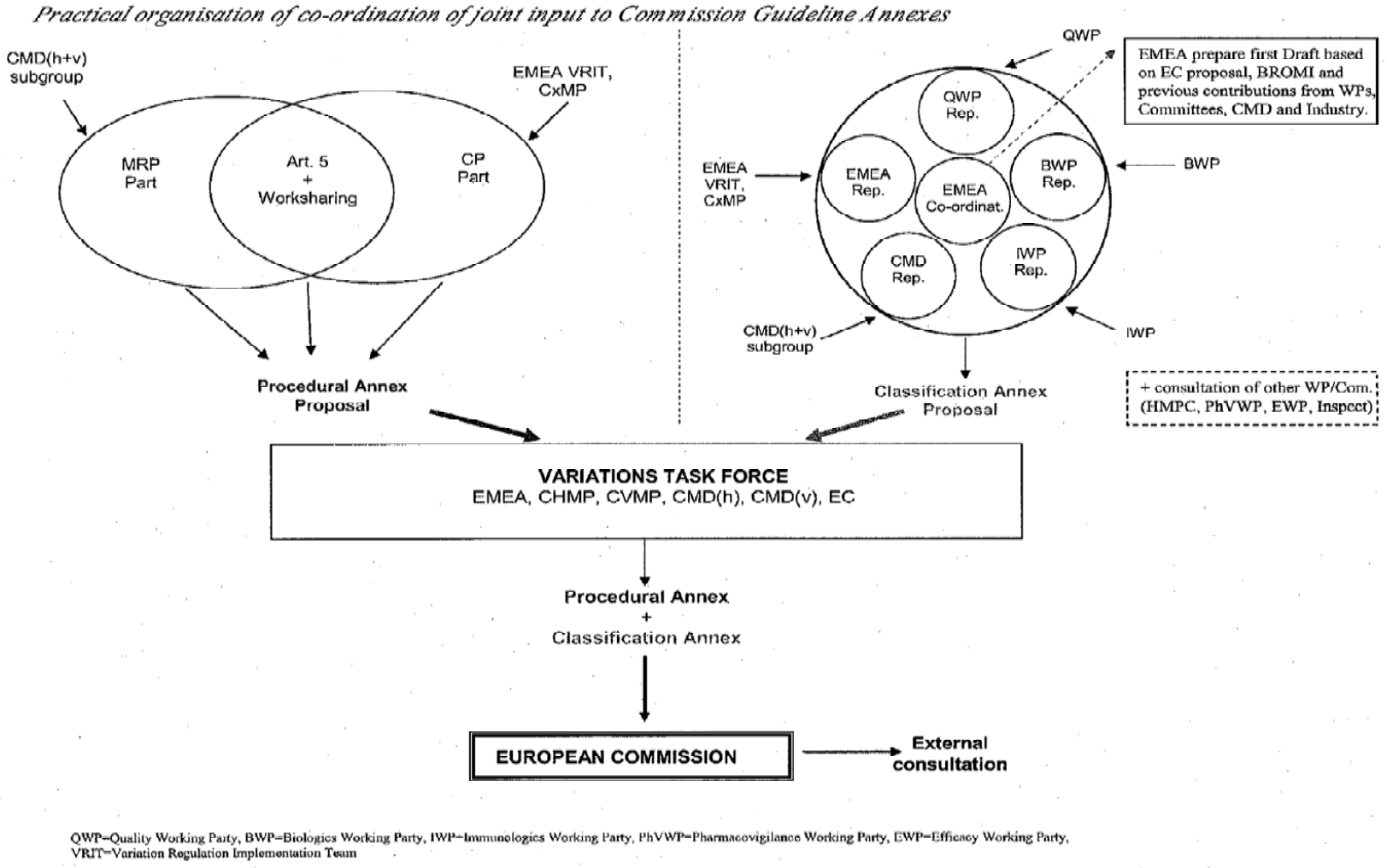
Background



QWP=Quality Working Party, BWP=Biologics Working Party, IWP=Immunologics Working Party, PhVWP=Pharmacovigilance Working Party, EWP=Efficacy Working Party, VRIT=Variation Regulation Implementation Team

Background

05/01/2010

FINAL Variation Guidelines published on EC Website

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/betterreg/pharmacos/classification_guideline_adopted.pdf

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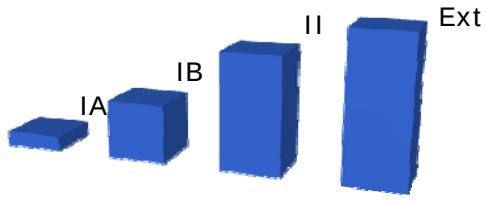
Types of Variations

- **Changes not requiring any prior approval**
  - Minor Type IA changes
  -Changes within an approved design space

- **Changes requiring prior approval**
  - Minor type IB changes
  - Major Type II changes
  - Extensions



Assessment to reflect level of risk

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Types of Variations

- **Type IA**

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

Type IA and Type IA_{IN}

- All "do and tell"
- Notify immediately – IA_{IN}
- Notify within 12 months of the implementation of the change – IA
- Rejection? – May be required to cease to apply change

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Types of Variations

- **Type II**

  Variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product

- **Type IB**

  Default category

  Variation which is not a type IA, type II or an extension.

Require prior approval

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Types of Variations

- Extensions – defined in Annex I of the Regulation (e.g. new pharmaceutical form) No real change. Similar to previous regulations

- Type IA and Type II – high level classification in Annex II of the regulation

- Classification guideline – detailed guidance on classification of types IA, IB and II

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- Guideline will now cover all aspects of MA dossier
- Type IA and Type IA_{IN} - Do and tell
- Type II's listed
- Type IB is now 'default' category
- No definitive list of IB – examples included
- Guideline can be regularly updated in light of scientific progress
- Pharmacovigilance - some now specified

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- **Guideline Format**

Introduction

a) Administrative Changes

b) Quality Changes

c) Safety, Efficacy, Pharmacovigilance changes

d) Plasma and Vaccine Antigen Master Files

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B. QUALITY CHANGES		**9**
I. Active Substance		**9**
a) Manufacture	1-5	9
b) Control of active substance	1-2	15
c) Container closure system	1-3	18
d) Stability	1	21
e) Design Space	1-3	23
II. Finished Product		**25**
a) Description and composition	1-6	25
b) Manufacture	1-5	31
c) Control of excipients	1-4	40
d) Control of finished product	1-3	44
e) Container closure system	1-7	47
f) Stability	1	54
g) Design Space	1-3	56
III. CEP/TSE/monographs	1-2	**58**
IV. Medical Devices	1-3	**61**
V. Changes to a marketing authorisation resulting from other regulatory procedures		**64**

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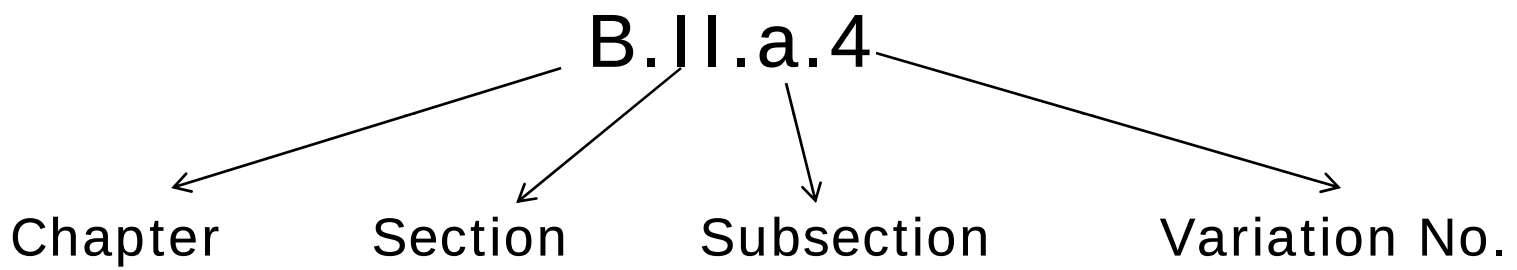
Variation Numbering system



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Introduction

- Definition of ‘specification parameter’ to incorporate its corresponding test method and limits
- Editorial changes do not require a variation and can be included in a variation concerning that part of the dossier.
- Compliance with updates to Ph. Eur. monographs.
- Changes to CEPs require variations to dossier where appropriate

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Type IA
Conditions and documents listed in guideline

- Administrative changes primarily type IA
  e.g. Change in ATC code, Deletion of (multiple) manufacturer (s)

- Some categories expanded to allow more minor changes as type IA or IAIN
  e.g. Changes in specification of active substance

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Type IB

Default category » therefore no conditions

- No definitive list but some **examples** included with list of documentation requirements
- Some IB examples will be familiar from previous guideline

  e.g. Changes in the composition of the finished product (B.II.a.3)
  - Expanded to allow possibility of type IA for very minor changes
  - Specifies several type II

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Type II
Listed in guideline - no conditions or documentation requirements

- Some type II familiar as previously 'default' when conditions not met. Some more specific.

  e.g. Change in site of manufacture (B.II.b.1 is type II for biologicals)
- Some type II completely new to guideline

  e.g. Update of dossier following referral (B.V.b.1)

  Real time or parametric release (B.II.d.3)

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B.II.e.5 Change in pack size of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the currently approved pack sizes	1, 2	1, 3	IA_{IN}
2. Change outside the range of the currently approved pack sizes		1, 2, 3	IB
b) Deletion of a pack size(s)	3	1, 2	IA
c) Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/ immunological multidose parenteral medicinal products.			II
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products		1, 2, 3	IB

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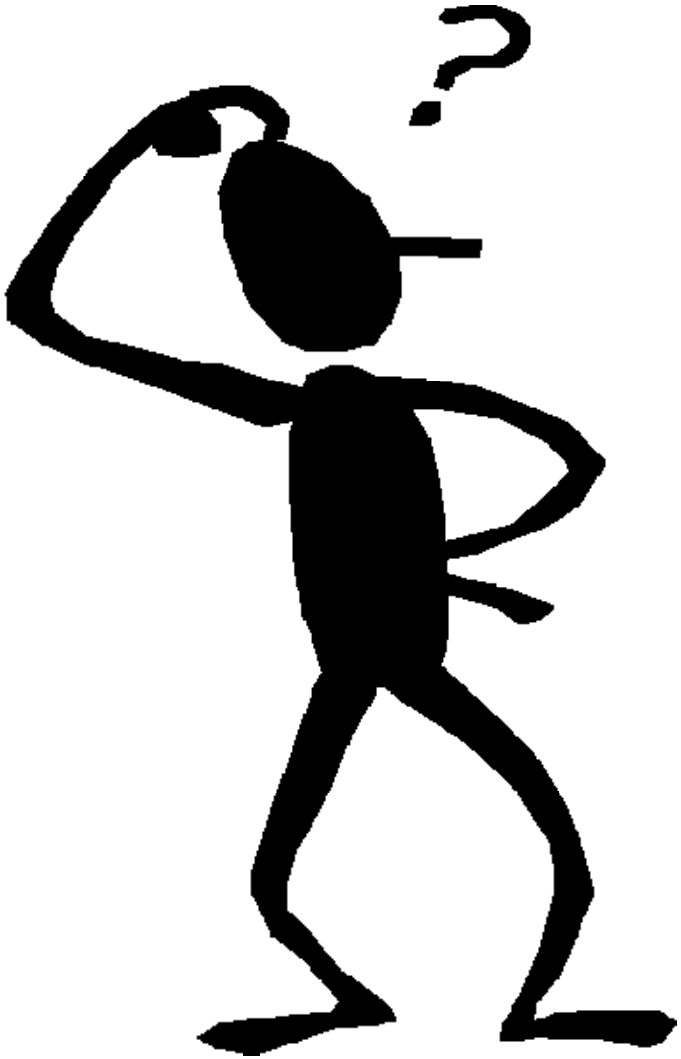

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- Submit under correct category
- Don’t include extra changes
- Fill in application form completely
- Address all conditions and data requirements
- Supporting documents must be legible
- If in doubt. Ask

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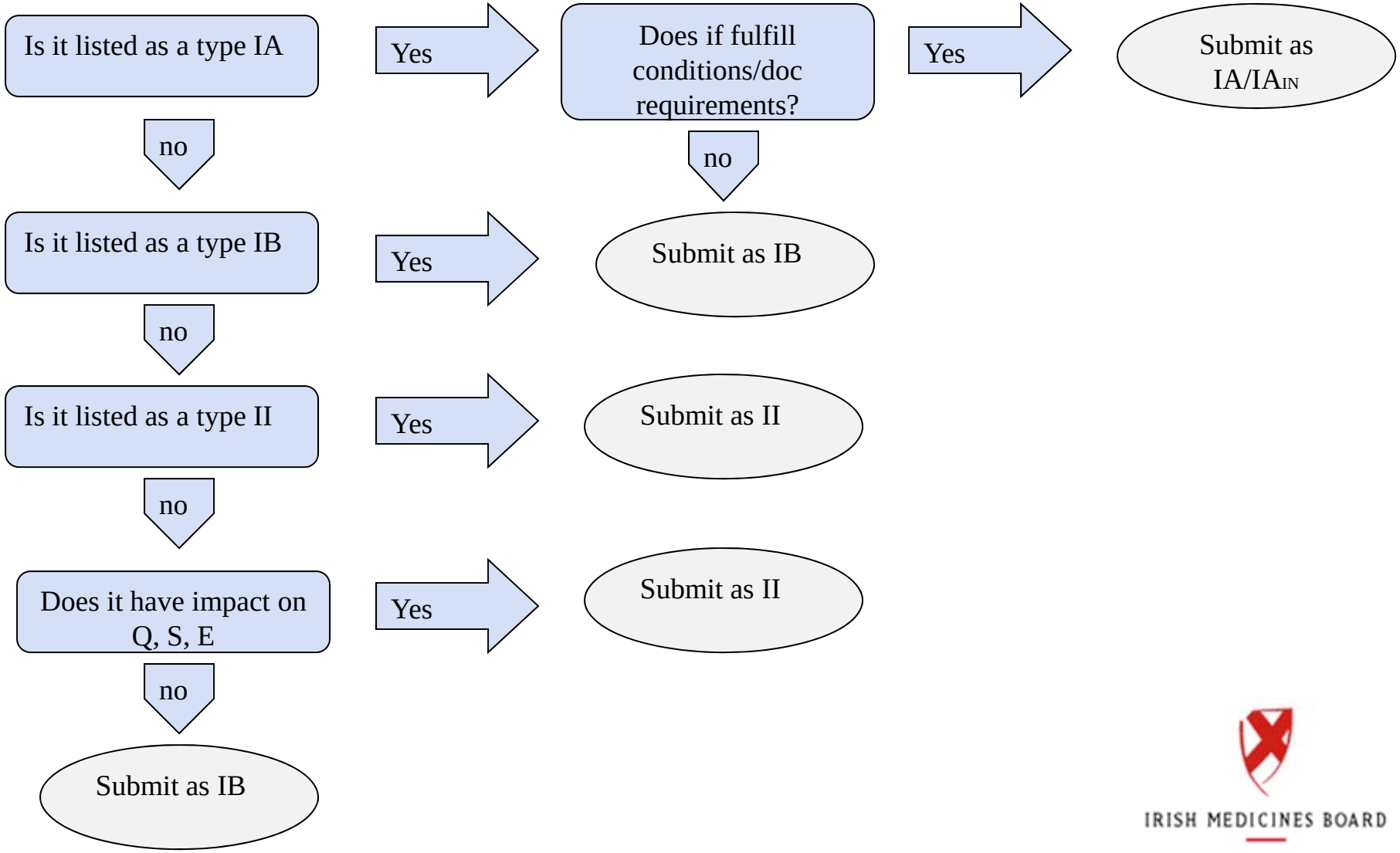

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Some Examples

Section B.I Active substance

Changes to manufacturing site – some IA (B.I.a.1)

- Minor changes to manufacturing process – IA (B.I.a.2)
- Addition of new test to specification – IA (B.I.b.1 and B.I.b.2)
- Deletion of a non-significant parameter – IA (B.I.b.1)
- Changes to packaging components – many IA (B.I.c.1 – B.I.c.3)

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Some Examples

Section B.II Finished Product

- Changes to manufacturing site for sterile products – IB (B.II.b.1)
- Minor changes to manufacturing process – IA for some oral dosage forms (B.II.b.3)
- Change in batch size for sterile product – IB (B.II.b.4)
- Addition of new test to specification – some IA (B.II.d.1 and B.II.d.2)

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Some Examples

Section B.II Finished Product

- Deletion of a non-significant parameter – IA (B.II.d.1)
- Shelf life reduction – IA (B.II.f.1)
- Shelf life extension – IB (B.II.f.1)
- Design space – B.II.g

  New = type II

  Changes within approved = no variation

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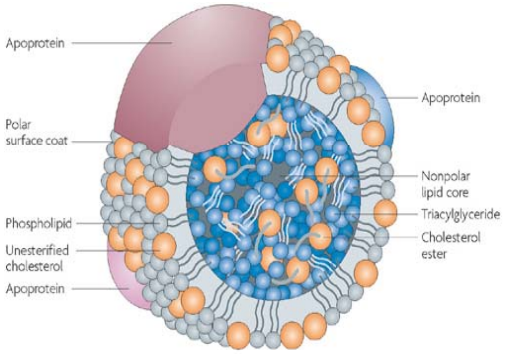
Some Examples

- Insufficient reclassification for Biologicals?
- They are complex
- There have been some changes

  - New CEP with viral safety

  - Change in scale without process changes

  - Change physiochemical tests methods for biological products



Nature Reviews | Drug Discovery

- Many remain as type II

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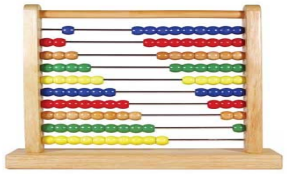
Impact

In 2006, EC announced its intention to make the variation regulations **simpler, clearer and more flexible**



Simpler ?

Clearer ?

More flexible ?

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Impact

- Transition phase will be difficult to manage
- Need to familiarise ourselves with new classifications
- New systems/workflows to be developed by industry and regulators
- Short implementation timeline

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Impact

- Simplified procedure for unclassified variations (IB default)
- Do and tell allows implementation of minor changes when needed
- Flexibility of ‘annual’ reporting
- Better use of MS resources
- Continual updating as experience is gained
- Same system for national and EU variations

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In summary

- The changes are substantial
- Correct classification is vital
- New system easier
- Risk based approach

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Thank you for your attention.

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