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Experiences with variations

Veterinary Medicines Information Day, 6th October 2011

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Overview of Presentation

- How to classify variations
  - Including unforeseen variations.
- Common errors with Type IA, Type IA_{IN}, Type IB and Type II variation applications.
- Some common procedures that are available

  for example
  - Grouping of variations,
  - Partnership Initiative.

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How to classify variations

- Variations are classified using the Variations Regulation Guideline published on European Commission website.

  - Link: http://ec.europa.eu/health/better-regulation-variations-regulations-developments_en.htm

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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

Conditions

1. New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics.
2. The primary packaging material remains the same.
3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate) including revised product information as appropriate.
2. Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of use as approved in the summary of product characteristics
3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).

Note: For B.II.e.5.c) and d), applicants are reminded that any changes to the 'strength' of the medicinal product require the submission of an Extension application.

How to classify variations

- What approach to take if the category is not appropriate for your change?
  - Use the “Z – other variation” category Note

    “Z – other variation” category, cannot be classified as a Type 1A variation unless an Article 5 recommendation has been published

NB:

Proposed classification subject to review by IMB

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How to classify variations – examples of "z" variations (1)

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product		Procedure type		
☐ a)	Tightening of in-process limits	☐ IA	☐ IB[9]	Implement. Date:
☐ b)	Addition of a new tests and limits	☐ IA	☐ IB[9]	Implement. Date:
☐ c)	Deletion of a non-significant in-process test	☐ IA	☐ IB[9]	Implement. Date:
☐ d)	Deletion of an in-process test which may have a significant effect on the overall quality of the finished product	II		
☐ e)	Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	II		
☐ f)	Addition or replacement of an in-process test as a result of a safety or quality issue	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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How to classify variations – examples of "z" variations (2)

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product		Procedure type		
☐ a)	Tightening of specification limits	☐ IA	☐ IB[9]	Implement. Date:
☐ b)	Addition of a new specification parameter to the specification with its corresponding test method	☐ IA	☐ IB[9]	Implement. Date:
☐ c)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐ IA	☐ IB[9]	Implement. Date:
☐ d)	Addition or replacement of a specification parameter as a result of a safety or quality issue	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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How to classify variations – examples of “z” variations (3)

B.II.c Change in control of excipients in the Finished Product	Procedure type	
☐ z) Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

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Article 5 –How does it work??

- By Marketing Authorisation Holder (MAH), National Competent Authority (NCA) of Member State (MS).

- Article 5 Recommendations are available to the public for reference on the Heads of Medicines Agency (HMA) webpage.
  - Link: http://www.hma.eu/293.html

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Examples of Published Article 5 recommendations:

Section of the Classification Guideline	Date issued	Summary of the proposed change	Proposed classification	Proposed conditions, where relevant
B.II.d.1.a	20.12.2010	Update of the dossier to comply with the provisions of a general monograph for the test of a finished product of the Ph.Eur. – Tightening of specification limits	IA	N/A
B.II.d.1.z	20.12.2010	Change in the microbiological purity specification parameters of the finished product to comply with Ph.Eur. A change to the finished products specifications in order to comply with Ph. Eur. could also possibly be acceptable as a Type IA notification in certain circumstances, taking into account the general acceptance that the new limits are acceptable for the specific dosage forms. It is up to the Applicant to provide all necessary data for the justification of the classification.	IB by default	N/A
B.III.2.z	23.05.2011	To reflect compliance with the Ph.Eur. and remove reference to the internal test method and test method number.	IA	N/A
B.II.f.1.z	24.01.2011	Change of stability protocol for annual stability	IB	N/A

B.II.d.1 Change in the specification parameters and/or limits of the finished product		Procedure type		
☐ a)	Tightening of specification limits	☐ IA	☐ IB[9]	Implement. Date:
☐ b)	Tightening of specification limits for medicinal products subject to Official Batch Release	☐ IA_{IN}	☐ IB[9]	Implement. Date:
☐ c)	Addition of a new specification parameter to the specification with its corresponding test method	☐ IA	☐ IB[9]	Implement. Date:
☐ d)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐ IA	☐ IB[9]	Implement. Date:
☐ e)	Change outside the approved specifications limits range	II		
☐ f)	Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	II		
☐ g)	Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue	IB		
☒ z)	Other variation	☐ IA ☒ IB ☐ II		☒ Art 5 Implement. Date: 20/12/2010

Article 5 recommendation web page

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

enter search phrase | search

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Heads of Agencies | **CMDh** | MRI Product Index | Directory

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Art.5 on Unforeseen Variations

- **Timetables 2011 for request to CMDh for a recommendation on the classification of an unforeseen variation - Article 5** (September 2010)

For the **template of the Article 5**, please refer to Variations

- **CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008** (June 2011)
- **CMDv Recommendations for Classification of Unforeseen Variations according to Article 5 of Commission Regulation (EC) 1234/2008**

Overview of Presentation

- How to classify variations
  - Including unforeseen variations.

- **Common errors with Type IA, Type IA_{IN}, Type IB and Type II variation applications.**

- Some common procedures that are available

  for example
  - Grouping of variations,
  - Partnership Initiative.

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Common errors with Type IA, Type IA_{IN}, Type IB and Type II variation applications

- Guideline page not submitted with the application form.
- Incorrect category chosen for the variation.
- Incorrect procedure type for the variation submitted.

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Common errors with Type IA, Type IA_{IN}, Type IB and Type II variation applications

- Missing documentation pertinent to the application.
- Insufficient supporting documents.

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Some common procedures that are available- Grouping of variations

- 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.
- CMDv Best Practise guide: Grouping

http://www.hma.eu/uploads/media/CMDv_BPG_016_on_Art_7_Grouping_11062009_EMEA-CMDv-366096-2009_Final__01.pdf

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Examples of “acceptable” Groupings (1)

- Introduction of a new manufacturer of the active substance that is supported by an ASMF (B.I.a.1.b - Type II).
- Change to comply with Ph. Eur. for active substance limits for related substance-For the already approved API manufacturer (B.III.2.a .1- Type 1A $_{IN}$).
- Change outside the approved specifications limited range of the finished product (B.II.d.1.e -Type II).
- Acceptable or not?

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Examples of “acceptable” Groupings (2)

- To change the shape of the tablets. (B.II.a.2.b - Type IB).
- To change the in-process controls (B.II.b.5.c & B.II.b.5.b-Type IA).
- To change the immediate packaging. (B.II.e.1.a.1-Type IA).
- Acceptable or not?

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Examples of “non-acceptable” Groupings (1)

- A MAH would like to remove in-process tests from 10 of its products.
- Products1-5 has the following in-process tests registered : Appearance, Assay, Related Substances & Identification.
- Products 6-10 has the following in-process tests registered : Appearance, Assay & Identification.

- Acceptable or not?

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Examples of “non-acceptable” Groupings (2)

- MAH would like to submit a Type II variation for a change in the manufacturing process of one of the manufacturers of the active substance. The MAH also wish to submit 7 x IA variations for new TSE certificates of suitability and 1 x IA to change the blister foil.

- Acceptable or not?

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Partnership Initiative –What is it?

- Worksharing Initiative between the UK's Veterinary Medicines Directorate, BE's Federal Agency for Medicines and Health Products and the IMB

- Aim:
  - to avoid duplication of work in evaluation of variations.

  - result in approval of the same data in dossiers for IE, BE and UK.

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Partnership Initiative –What is it?

Procedure	Eligible products	Technical assessment	Impact on SPC / product literature	Comment
Partnership Initiative	Nationally authorised	Yes	Yes	Co-ordinated technical assessment not limited to SPC/labelling issues

Clarification paper available on IMB website.

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Partnership Initiative – Advantages.

- Reduced administrative burden.
- Assessment to defined timetable with consolidated list of questions produced.
- Can include changes to SPCs/labels/leaflets, changes in shelf-life, changes in the manufacturing process and changes to withdrawal periods.
- Scope is Type II variations possible extension to Type 1B applications.

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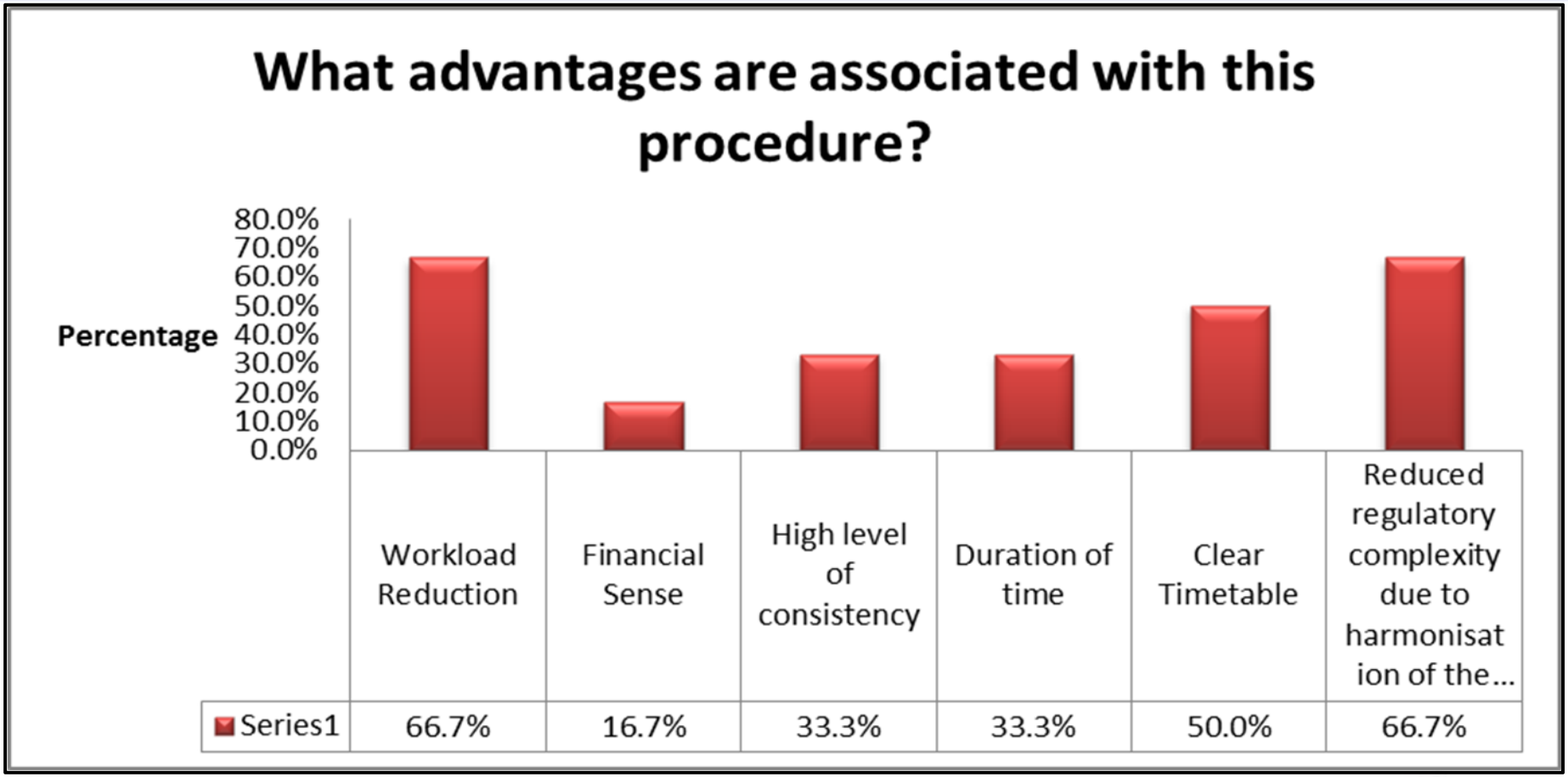
Partnership Initiative –Advantages.



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Partnership Initiative – recognized issues.

- Unacceptable or uncertain long timelines.
- Not enough time for responses to be resolved.
- Less informal contact with assessors.
- Delay in setting timetables.
- Increased regulatory requirements.

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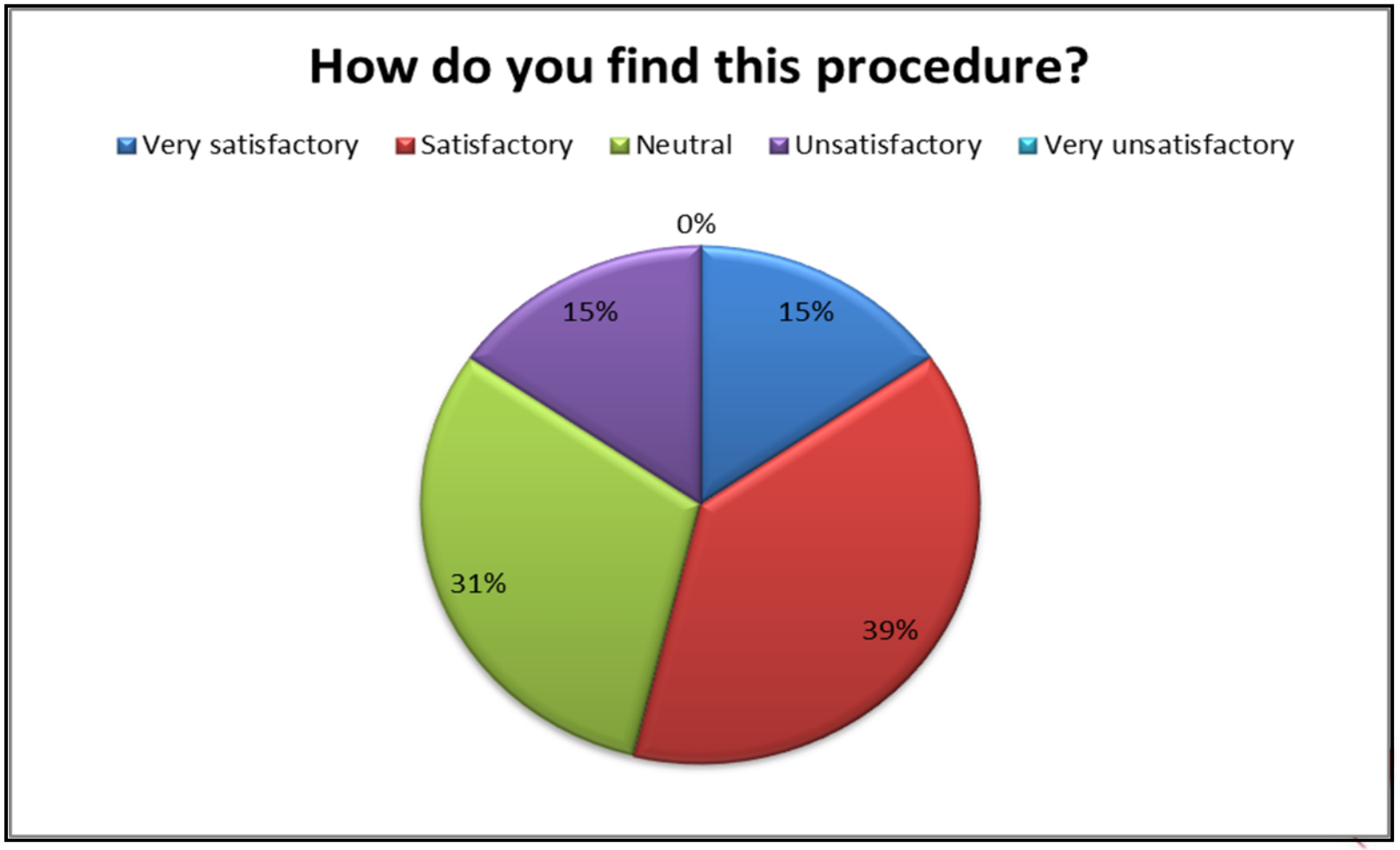
Partnership Initiative



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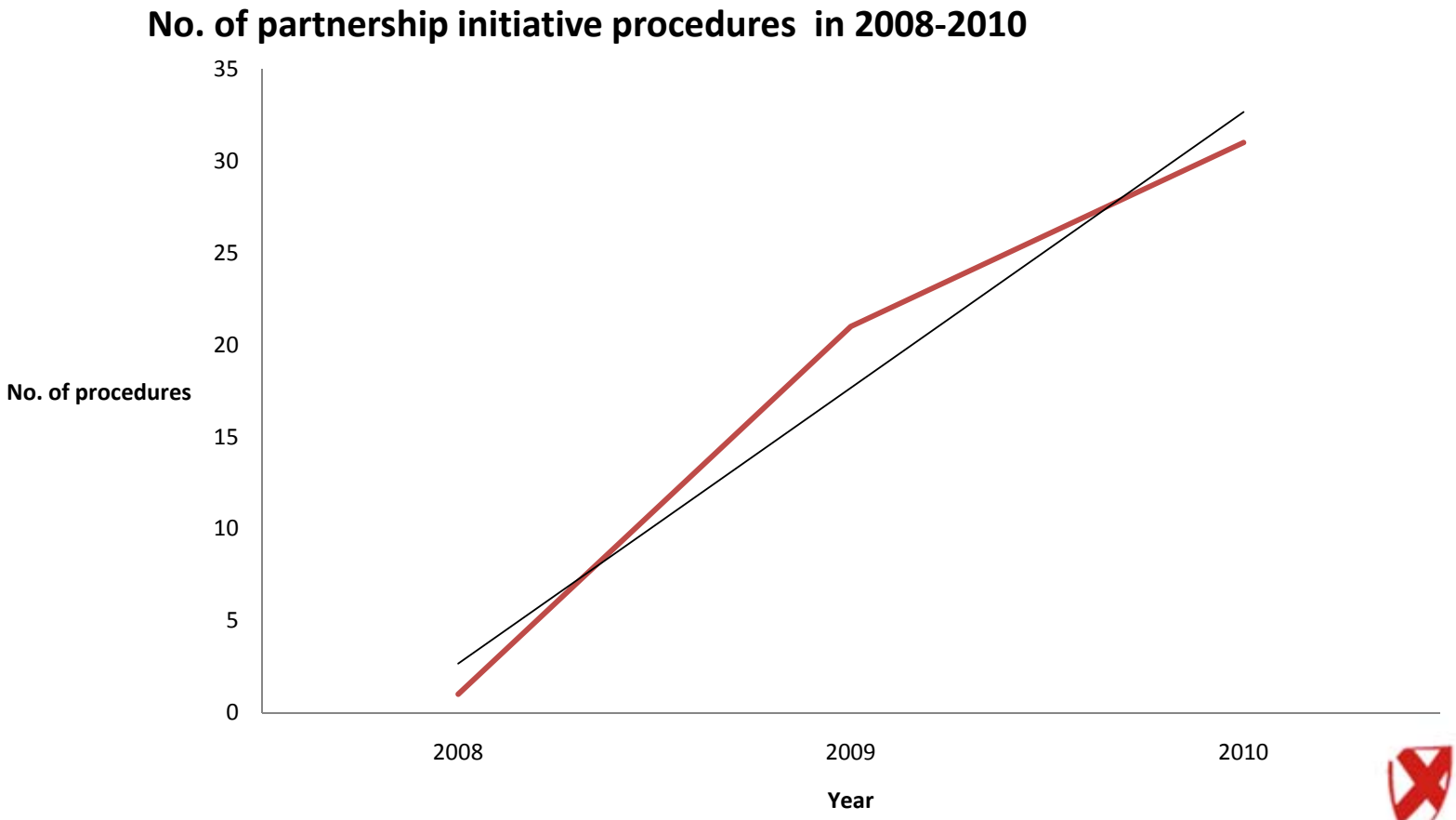
Partnership Initiative



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Closing Remarks

- Further information is available on the following websites:
  - www.imb.ie
  - http://ec.europa.eu/health/better-regulation-variations-regulations-developments_en.htm
  - http://ec.europa.eu/health/documents/eudralex/index_en.htm
  - http://www.hma.eu/293.html
  - CMDv Best Practise guide: Grouping http://www.hma.eu/uploads/media/CMDv_BPG_016_on_Art_7_Grouping_11062009_EMEA-CMDv-366096-2009_Final__01.pdf

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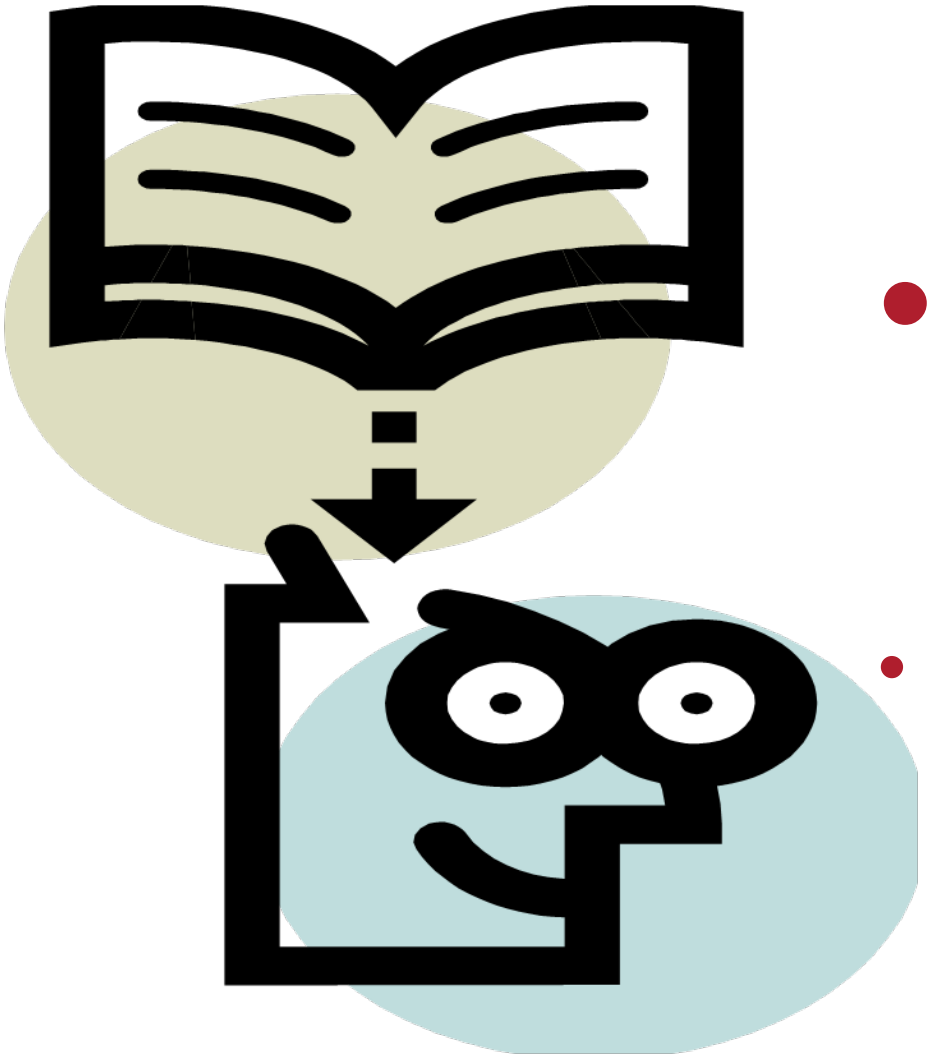

- Questions?

- Contact us at vetinfo@imb.ie

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