New Variations Regulation 6 months experience NCA & CMDh

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What is a „Variation“?

Any amendment to the documentation - which is the legal basis for the marketing authorisation of the medicinal product - submitted to the competent authority.

three possibilities to amend the documentation:
- to change the content of a document
- to add a document
- to delete a document

General Rule:

amendments to documents/details which are not part of the documentation do not trigger a variation

History of the Variation Regulation(s)

	Mutual Recognition	Central MA
1.	CR No 541/95	CR No 542/95
2.	CR No 1146/98 (amendment)	CR No 1147/98 (amendment)
3.	CR No 1084/2003	CR No 1085/2003

4. COMMISSION REGULATION (EC) No 1234/2008
entry into force on 01 January 2009

applies from 01 January 2010

CR = Commission Regulation (EC)

Reminder ….

The history of the Variation Regulation is an Evolution !

Your knowledge of the past system is the backbone for the future system

Do you really know the possibilities of the 'old' Variation Regulation (CR (EC) 1084/2003)?

New Type of Legislation

- describe the basic procedures
- set the framework for options

This results in the need of…

- more procedural knowledge
- better educated personal
- strategic thinking in a workplan
- to take responsible decisions

strengthen the role of Drug Regulatory Affairs

We / You have asked for ….

- Simplification and flexibility
- Type IB by default

This is addressed by ….

- Two fundamental changes
  - Type IB by default
  - Do and Tell for Type IA

- Two options
  - Grouping (and ‘European Annual Report’)
  - Worksharing

Commission Regulation (EC) 1234/2008

Scope of the Variation Regulation

As the ‚old' one – no change

- ex-concertation/MRP/DCP
- following harmonisation (Article 30 and 31(1))

for **authorised** medicinal products

Outside:

- Change (transfer) of the MAH

C. Safety, Efficacy, PharmVigilance

C.I.8 Introduction of a new Pharmacovigilance system	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) which has not been assessed by the relevant national competent authority/EMEA for another product of the same MAH			II
b) which has been assessed by the relevant national competent authority/EMEA for another product of the same MAH*		1	IB
Documentation			
1. The new Detailed Description of the Pharmacovigilance System (DDPS)			
*Note: This variation covers the situation where the applicability of an already assessed Pharmacovigilance System will have to be assessed for the new MAs concerned (e.g. at time of transfer of MA).			

… and CMDh Q&A-List:

Question 2.8

In case the MAH in one member state is changed, is a variation in all member states necessary to introduce the new pharmacovigilance system of the new MAH or is a purely national variation in the member state concerned sufficient?

…

Directive 2001/83/EC
of 6 November 2001

Article 35(1)

Any application by the marketing authorization holder to vary a marketing authorization which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the medicinal product concerned.

The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

… and CMDh Q&A-List:

… cont.

Answer:

According to C.I.8 in case of the transfer of a MAH in one member state the pharmacovigilance system of the new MAH has to be submitted to all member states concerned as variation type IB (in case the pharmacovigilance system has already been approved for a different product) or type II (in case the pharmacovigilance system has not yet been assessed). However, the transfer of the MA to a new MAH is to be handled as an independent purely national application according to Art. 1(2) of the Regulation (EC) 1234/2008.

… and ‘Examples for Grouping‘

EXAMPLES FOR ACCEPTABLE AND NOT ACCEPTABLE GROUPINGS FOR MRP/DCP PRODUCTS

Doc. Ref: CMDh/173/2010
May 2010

For future variation applications comparable to those listed below as acceptable groupings applicants do not have to contact the RMS for acceptance as these grouped applications are already accepted by all EU member states.

1. ACCEPTABLE GROUPINGS

…

- After a transfer of the MA in one or more member states to a new MAH – which itself is an independent purely national application – **all other changes related to that transfer**, e.g. *change in product name in that member state, new DDPS for the new MAH etc*. **may** be grouped in one application according to the highest variation type for the single changes.

CMDh: Variations

BfArM
Federal Institute for Drugs and Medical Devices

Variation Procedure

In order to view some of the documents on this website you need **Acrobat Reader** (click here to download)

- **Draft Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedure** (Revision 6, October 2009)
  Click here
  Note: *The Revision 6 of the Best Practice Guides for the Submission and Processing of Variations in the Mutual Recognition Procedure, taking into account Commission Regulation No 1234/2008, is published as a draft document and subject to review following the publication of the relevant Commission guidelines.*

- **Timetables for request to CMD(h) for a recommendation on the classification of an unforeseen variation - Article 5** (April 2009)
  Click here

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

  For the **templates Type II variation** ´Preliminary Variation Assessment Report´ and ´Type II variation Final Variation Assessment Report´, please refer to Assessment Report

- **European Medicines Agency/CMDh explanatory notes on Variation Application Form** - Human medicinal products only (January 2010)
  Click here

- **Common grounds seen for invalidation/delaying day 0 for Variations** (September 2008)
  Click here

- **Cover letter for Variation Applications in the Mutual Recognition Procedure** (Latest update: December 2009)
  Click here

- **Questions & Answers - List for the Submission of Variations according to Commission Regulation (EC) 1234/2008** (January 2010)
  Click here

- **Implementation of Variation Regulation 1234/2008 in each Member State for Medicinal Products authorised by purely national procedures** (January 2010)
  Click here

CMDh BEST PRACTICE GUIDES FOR THE SUBMISSION AND PROCESSING OF VARIATIONS IN THE MUTUAL RECOGNITION PROCEDURE (May2010) (Rev8)

TABLE OF CONTENTS

CMD(h): Q/A-LIST FOR THE SUBMISSION OF VARIATIONS ACCORDING TO COMMISSION REGULATION (EC) 1234/2008

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh-132-2009-Rev1-Clean_2010_01_Q_A_variation.pdf

- replaced the existing (old) Q/A-list
- will be updated on a regular basis …
- new structure
  1. General questions
  2. Questions relating to the submission of variations
  3. Questions relating to the Classification of variations
  4. Questions relating to grouping and worksharing
  5. Questions regarding the approval and implementation of variations

Scope of the Variation Regulation

As the ‚old' one – no change

- ex-concertation/MRP/DCP
- following harmonisation (Article 30 and 31(1))

for **authorised** medicinal products

Outside:

- Change (transfer) of the MAH
- changes to **registered** homeopathic and traditional herbal medicinal product (despite they are eligible for the MRP/DCP)

Article 2 - Definitions

- Minor variation type IA
  minimal impact on quality, safety and efficacy
- Major variation type II
  significant impact on quality, safety and efficacy

} *Annex II*

- Extension of a MA
  - as a change to a MA
  - as a new MA

} *Annex I*

- Minor variation type IB
  neither type IA nor type II nor extension

„Type IB by default“

- defined list for Type IA, II and line extension
- agreed examples of Type IB in the ‚Categorisation Guideline‘ (Article 4)
- unlisted changes are by definition Type IB

but,

if during the validation the CA consider a significant impact on quality, safety or efficacy, the application is considered a Type II variation

Experience ?

Definition - Classification Guideline

"When one or more of the conditions established in the Annex to this Guideline for a minor variation of Type IA are not met, the concerned change may be submitted as a Type IB variation unless the change is specifically classified as a major variation of Type II."

… and CMDh Q&A-List:

Question 3.1

Which Type of variation should be submitted when the particular change we are applying for is not mentioned in the classification guideline or one or more of the conditions cannot be fulfilled?

Answer:

If a change is not mentioned in the Annex II of the Variation Regulation (EC) 1234/2008 or the classification guideline or the conditions for a specific change could not be fulfilled and the change is not already classified as a Type II variation, this change can be submitted as a Type IB variation by default. However, if the change in the view of the applicant has a significant impact on quality, safety and efficacy of the product, a Type II variation has to be submitted.

Classification Guideline – practical example

B.II.c.2 Change in test procedure for an excipient			Conditions to be fulfilled	Documentation to be supplied	Procedure type
	a)	Minor changes to an approved test procedure	1, 2, 3, 4	1, 2	IA
	b)	Deletion of a test procedure if an alternative test procedure is already authorised.	5	1	IA
	c)	Replacement of a biological/immunological test method or a method using a biological reagent			II
	d)	Other changes to a test procedure (including replacement or addition)		1, 2	IB

	Conditions	
	5.	An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

- If Type IA condition not met
  and
  If not listed as a Type II

→ **'Default' Type IB**

~~**'Unforeseen' Variation**~~

Variation Application Form

… how to address this ?

B.II.c.2 Change in test procedure for an excipient			Procedure type		
☐	a)	Minor changes to an approved test procedure	☐IA	☐IB[9]	Implement. Date:
☐	b)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB[9]	Implement. Date:
☐	c)	Replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent	II		
☐	d)	Other changes to a test procedure (including replacement or addition)	IB		

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

… to customize the change

B.II.c.2 Change in test procedure for an excipient			Procedure type		
☒	b)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☒IB[9]	Implement. Date:

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

… and copy it into the variation application form

Article 5 – Unforeseen Variations - (1)

… cont.

alternative:

- MAH (or NCA) can ask the CMD (national MA) or the Agency (central MA) for a scientific recommendation on the classification of unlisted changes (Article 5)
- guidances with timelines and application form is published
  - http://www.hma.eu/96.html
  - http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Templates/Variations/CMDh_139_2010_Rev1_May10.pdf

Article 5 – Unforeseen Variations - (2)

- scientific recommendation within 45 days from CMD or Agency
- to be consistent with Article 4 Guideline
- CMD(h)/CMD(v) and Agency shall cooperate
  - coherence of recommendations
  - publish the scientific recommendations following deletion of commercial confidential informations (and this will effectively lead to an update of the Guidelines)

Article 5 – Unforeseen Variations - (3)

You are here: Human Medicines > CMD(h) > Procedural Guidance > Art 5 recommendations

- About CMDh
- Statistics
- Press Releases
- **Procedural Guidance**
  - General Info
  - Application for MA
  - eSubmissions
  - Generics
  - Applicant´s Responses
  - Renewal
  - Variation
  - **Art 5 recommendations**

Art.5 on Unforeseen Variations

- **CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008** (April 2010)
  Click here

First recommendations at the March CMDh

- 4 requests – 3 x Industry / 1 x NCA
- 2 recommendations by consensus
- 2 recommendations by majority vote

Article 5 – Unforeseen Variations - (4)

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

CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008

Section of the Classification Guideline	Date issued	Summary of the proposed change	Proposed classification	Proposed conditions, where relevant
To be confirmed	22.03.2010	Additional procedure for analysis of the breath test.	II	N/A
B.II.c.1 z) Other variation	22.03.2010	Change in specification of the excipient Maltose from in-house to USP monograph (Maltose monohydrate). LAL test will continue to be carried out as additional specification as required by the monograph of the Ph.Eur.	IB	N/A
B.II.b.3	22.03.2010	Change in the manufacturing process of the finished product: minor change in the manufacturing process of modified release oral dosage form.	**IB by default**	N/A
C.I.10	22.03.2010	Submission of results of assessments carried out on target patient groups in order to comply with Article 59(3) of Directive 2001/83/EC and any resulting change to the Package Leaflet.	IB[1]	N/A

Article 5 – Unforeseen Variations - (5)

Section of the Classification Guideline	Date issued	Summary of the proposed change	Proposed classification	Proposed conditions, where relevant
N/A	26.04.2010	Deletion of product name from list in PL, following withdrawal of MA in the relevant CMS.	**Article 61(3) notification**	N/A
B.I.a.1.z	26.04.2010	Add an alternative sterilisation (gamma irradiation) site for the active substance.	**IB by default**	N/A
B.II.b.3.z	26.04.2010	Minor change in the manufacturing process of the finished product- Change in the holding time of an intermediate.	**IB by default**	N/A
B.II.b.3.b)	26.04.2010	Change in the manufacturing process of the finished product: to move the sterilising filtration from A or B to C.	**IB by default**	N/A
B.II.b.3	26.04.2010	Change in the manufacturing process of the finished product: minor change in the manufacturing process of solution for injection/infusion.	**IB by default**	N/A

Article 5 – Unforeseen Variations - (6)

Report from the CMDh meeting held on 19th and 20th April 2010

"Marketing Authorisation Holders are reminded that the classification guideline should be carefully checked before a request for classification in accordance with Art. 5 is sent to the CMDh. **The CMDh would remind applicants that the default position is a type IB variation**.

Attention is drawn to the text in the Commission Guideline "When one or more of the conditions established in the Annex to this Guideline for a minor variation of type IA are not met, the concerned change may be submitted as a type IB variation unless the change is specifically classified as a major variation of type II."

NO CHANGES …

… **how to run the procedures**

- Type IB Variation
- Type II Variations
- Line extensions
- Variations to human influenca vaccines
- Urgent Safety Restriction

! NO CHANGE !

Type IA Variations – (1)

- „**Do** and Tell“ - implemented by the MAH before notification to CA (Article 8(1)):

  “Where a minor variation of type IA is made, the holder shall submit simultaneously to all relevant authorities a notification containing the elements listed in Annex IV. This notification **shall be submitted** within 12 months ***following the implementation of the variation***.

  *However, the notification **shall be submitted** immediately **after the implementation of the variation** in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.”*

Type IA Variations – (2)

- reporting to CA either
  - immediately (for defined Type IA eg change of address, …)
  - all others within 12 month at latest (no fixed date)
  - validation procedure only
  - timetable of **30 days**

The most discussed phrase is …

‚implemented by the MAH‘

… and CMDh Q&A-List:

Question 5.2

What is meant by “implementation” for Type IA variations?

… and CMDh Q&A-List:

Answer:

For **quality changes**, implementation is when the Company makes the change in its own Quality System.

…

For changes to the **pharmacovigilance system** (DDPS), 'implementation' is when the Company makes the change in its DDPS (i.e. when it internally approves the DDPS incorporating the changes).

For **product information**, it is when the Company internally approves the revised product information. The revised product information will then be used in the next packaging run.

Two further Key Definitions …

Grouping

what to place in one application *Annex III*

Worksharing

who and how to evaluate an application

→ therefore worksharing on a grouped application is an option for the applicant

Type IA Variations

Article 7

Grouping of variations

1. Where several variations are notified or applied for, a separate notification or application as laid down in Chapters II, III and IV shall be submitted in respect of each variation sought.
2. By way of derogation from paragraph 1, the following shall apply:

(a)where **the same minor variations of type IA** to the **terms of one** or **several** **marketing authorisations owned by the same holder** are notified at the same time to the same relevant authority, a single notification as referred to in Articles 8 and 14 may cover all such variations;

Grouping of Type IA Variations – (1)

- **2-dimensional matrix**
  - several changes to one MA
  - identical change to several MA‘s
  - (several identical changes to several MA)

  at the same time for the same MAH

- **!!!! very complicated structures can be created !!!!!**

Definition of a Marketing Authorisation

… different definitions by CA

a MA is containing

- one strength
- all strength of the medicinal product

→ agreed definition by CMD(h) (and confirmed by EC) for running the variation procedure:

  – a MA is defined by the **Medicinal Product Number** of the MR-Number

    e.g. DE/H/**1000**/001-010

… and CMDh Q&A-List:

CMDh Q/A-LIST …

Question 1.4

Is it possible to submit an identical variation for different pharmaceutical forms and/or strengths of a marketing authorisation as a single application?

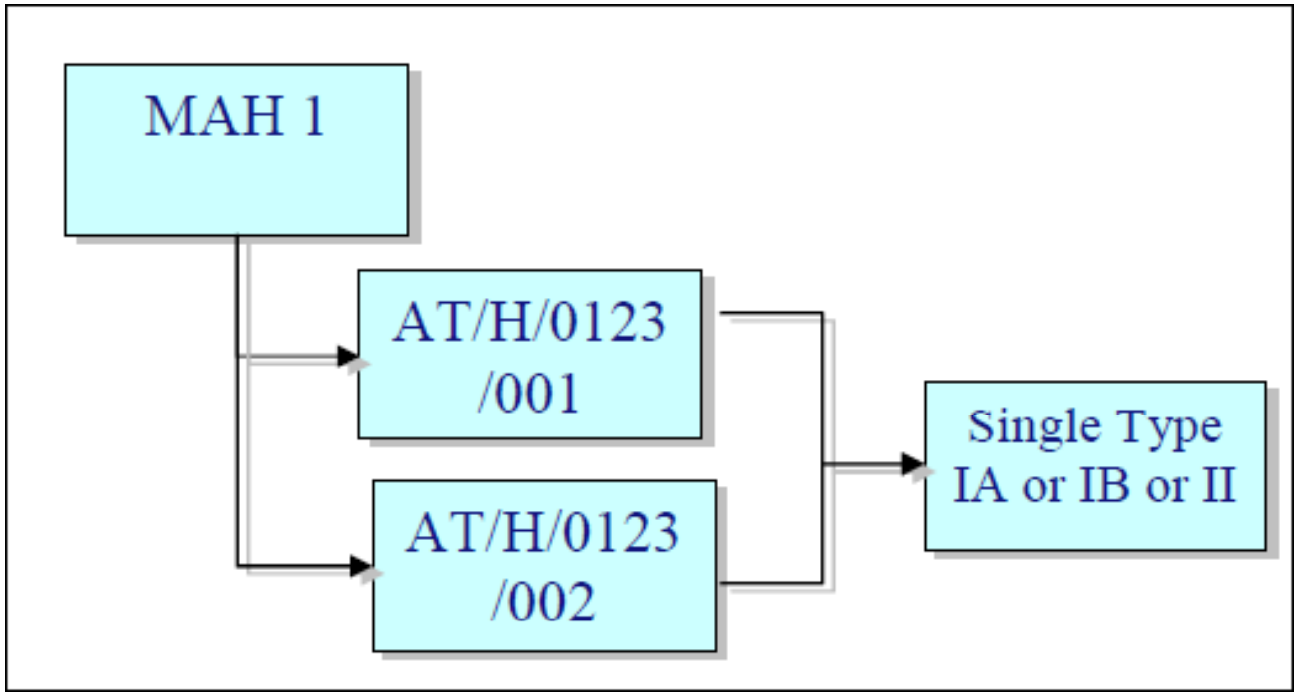
Answer:

For variation applications, the following definition of a marketing authorisation is used: all strenghts and/or pharmaceutical forms of a certain product.

… and consequences:

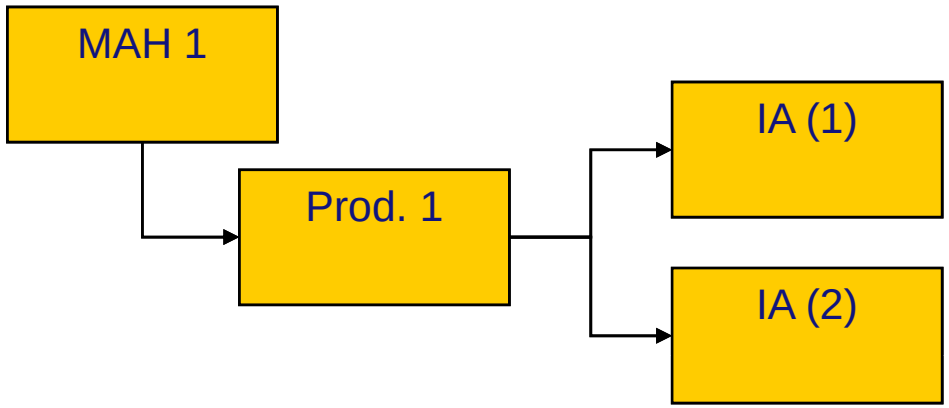
cont.

The following is an example of a single application:



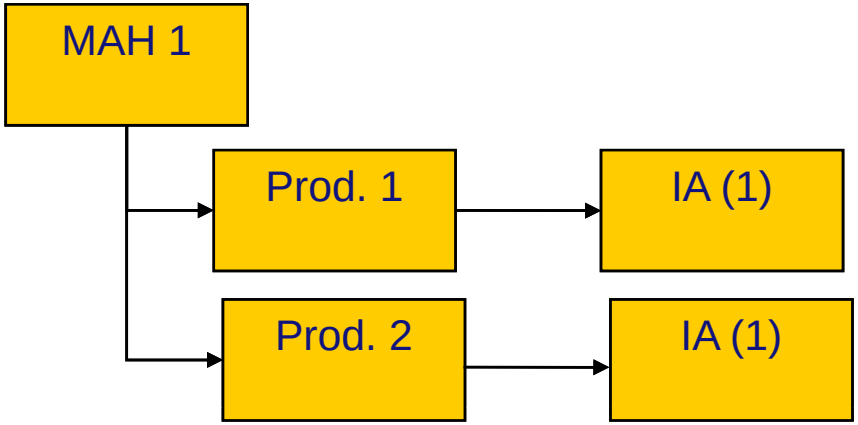
Grouping of Type IA Variations – (2)

- More than one Type IA or IA_{IN} affecting one medicinal product
- "Annual" report is a specific form of grouping for Type IA Variations



Grouping of Type IA Variations – (3)

- One Type IA or IA_{IN} affecting more than one medicinal product from the same MAH
- procedure number to be requested from RMS



… and CMDh Q&A-List:

Question 4.9

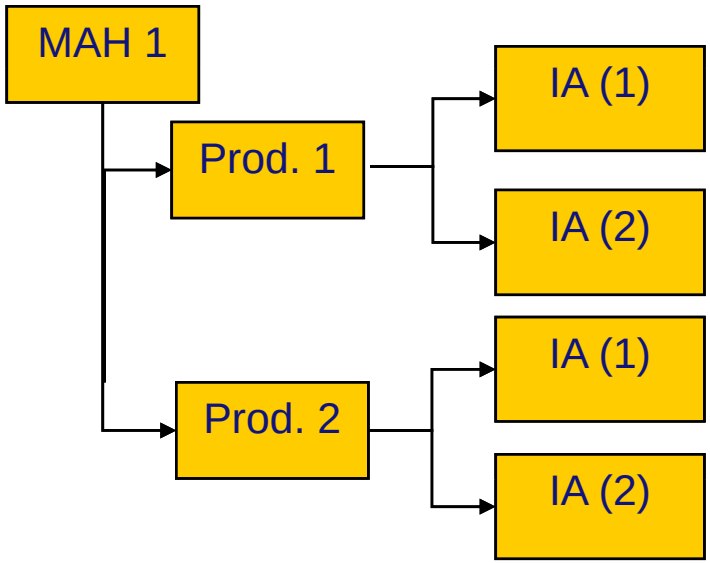
A product is registered through MRP/DCP. Is it possible to submit a change in the name and/or address of the marketing authorisation holder (variation A.1, type IAIN) in more than one MS as a grouped application concerning one marketing authorisation, even if the name and/or address is different in each MS?

Answer:

A change in the name and/or address of the marketing authorisation holder in more than one MS of a MRP/DCP marketing authorisation can be submitted as a grouped application consisting of several type IA variations.

Grouping of Type IA Variations – (4)

- More than one **identical** Type IA and/or IA_{IN} affecting more than one medicinal product from the same MAH (so-called "supergroups")



Type IA-Grouping accross MA …

- How is the case in this example if several RMS are involved:
  - DE/H/1001/001-003/DC
  - DK/H/3003/001-005/MR
- legally possible as the Regulation is addressing MA and MAH and not MS

B U T

not all possibilities are used by a wise woman/man

!!!!!!!!

Type IA-Grouping accross MA …

Practical experience I:

- a MAH has asked the CMDh for a worksharing for Type IA
- request was dismissed by the CMDh, due to legal reasons as Type IA variations are excluded from worksharing

Type IA-Grouping accross MA …

Practical experience II:

- a MAH has asked DE (RMS) how to submit the corresponding Variations to implement the outcome of the Commission Decision for an Article 30 Referral?
  - one RMS
  - 7 MRP Duplicates
  - Labelling: C.I.1 as Type IA_{IN}
  - Module 3: B.V.b.1 as Type IA_{IN}
- one Type IA_{IN} application (grouping across all MA) is acceptable. Workable for the MAH (eCTD)?

… and CMDh Q&A-List:

Question 4.6

Is it possible to group Type IA variations for a CP and a DCP product if the Rapporteur and RMS are from the same Competent Authority?

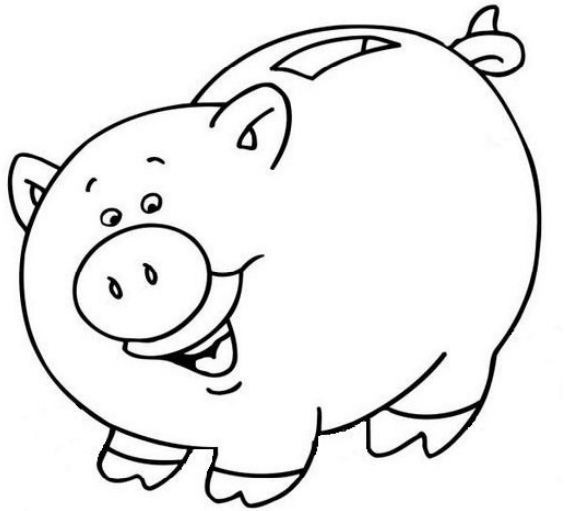
Answer:

No, CP and MRP/DCP products may only be combined in a worksharing procedure, not in any other type of procedure.

Annual Report

- nothing in common with the FDA Annual Report
- Grouped applications consisting of only Type IA variations
- can be submitted at any point in time but at the latest 12 months after implementation of first TypeIA change
- can include Type IA and IA_{IN} (the latter to be submitted immediately)
- no need to be related/consequential
- it‘s an option to the MAH

The Piggy Bank …



… works with simple rules

- do I like to save ?
- if a Piggy Bank is broken, go to the bank …

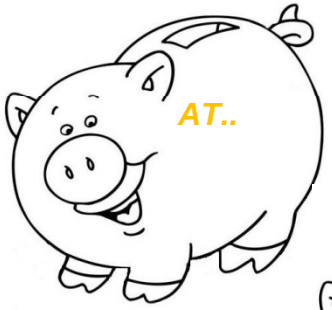
Annual Report and the Piggy Bank

Type IA

Fuse

(max. 12 months)

or



Grouping for Type IB – II - EA

- several changes to one MA

  at the same time for the same MAH

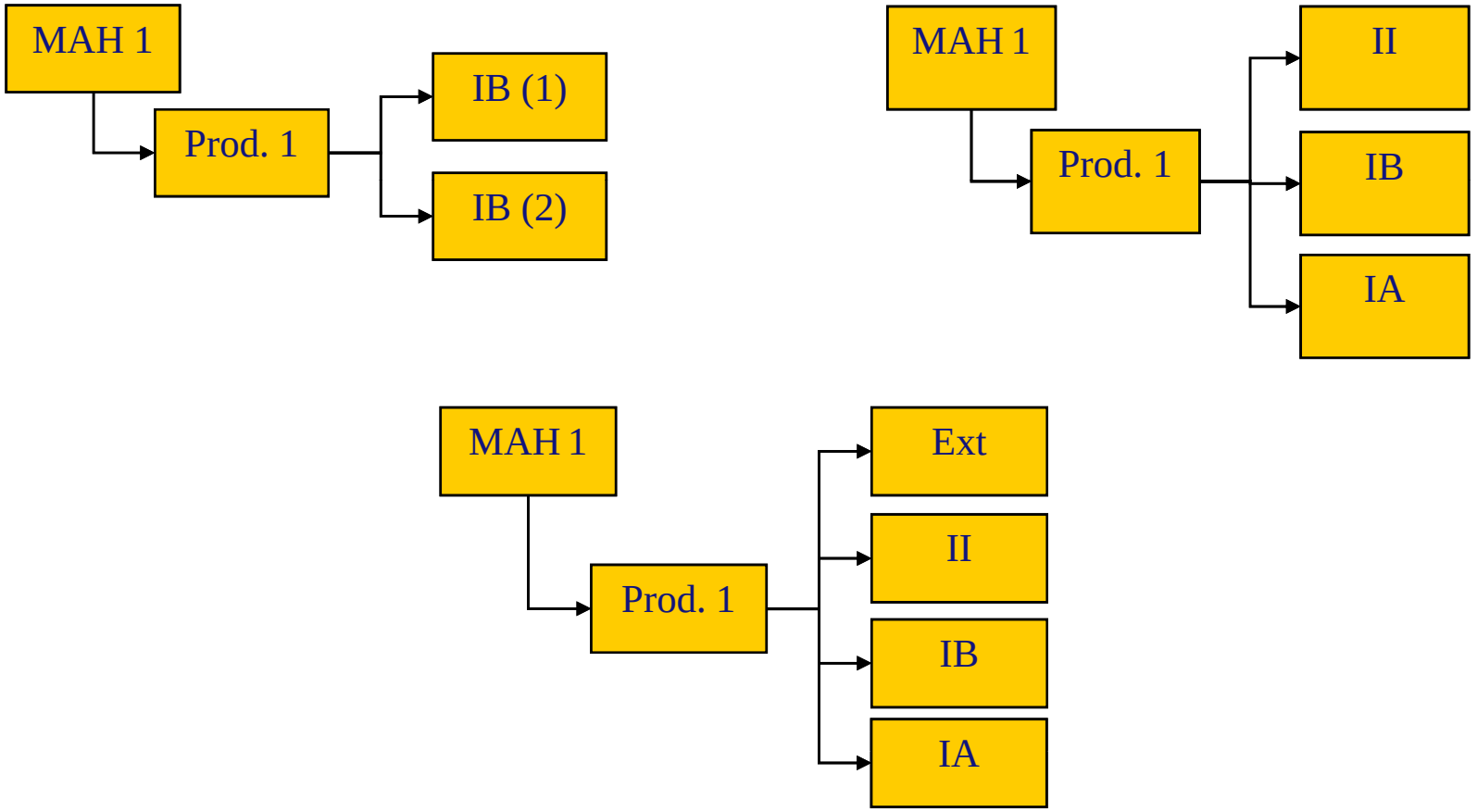
- classification of the grouped submission according to the highest level of the individual submission type

- **optional** for the MAH

  all or nothing approach?

  No, as you submit an application, but CA grant a variation

Grouping of Extensions, Type II / IB / IA Variations



… and CMDh Q&A-List:

Question 4.8

A product is registered through MRP/DCP. Is it possible to submit a change in the product name (variation A.2.b, type IB) in more than one MS as a grouped application concerning one marketing authorisation, even if a different product name in each MS is used?

Answer:

A change in the product name in more than one MS of a MRP/DCP marketing authorisation can be submitted as a grouped application consisting of several type IB variations (even if a different product name in each MS is proposed), since it falls under situation 4 listed in Annex III of the Variation Regulation (all variations in the group relate solely to changes of administrative nature to the SmPC, labelling and package leaflet).

Type IB Grouping or „Umbrella Type II‘

Restart of discussion:

see CMDh Examples for acceptable and not acceptable Groupings for MRP/DCP Procucts

“The update of Module 1 incl. User Test, Braille, Environmental Risk Assessment, DDPS, RMP, QPs declaration etc., e.g. in preparation of a Repeat Use MRP **may be submitted as one single application according to type II**. The change may be introduced under classification category C.I.z – Update of Module 1 in preparation of a RUP.”

Worksharing - (1)

- for „… several MA‘s owned by the same holder.“
- for Type IB, Type II and grouped variations, but not for extension applications

- Coordination
  - Agency - if one central MA is included
  - CMD (h/v) - in all other cases

- Evaluation (‚reference authority‘)
  - Agency: Scientific Committees eg. CHMP
  - CMD: CA of a MS concerned, chosen by CMD taking into account a recommendation by the MAH

Worksharing - (2)

- Presubmission information submitted > 2 weeks in advance of CMDh meeting

  ⇨ decision will be taken at next CMDh
- If presubmission information submitted < 2 weeks in advance of CMHh meeting

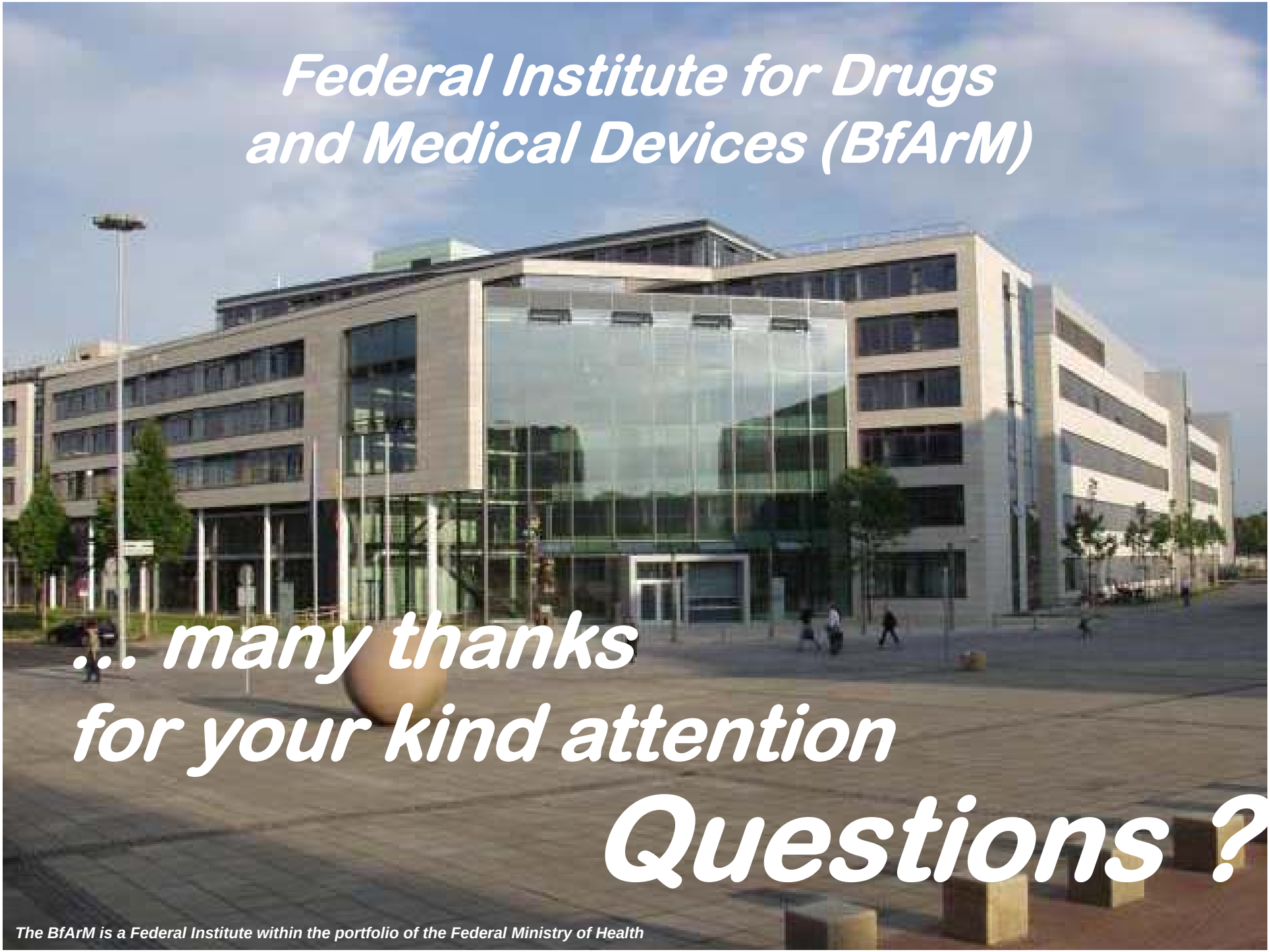
  ⇨ decision will be taken at the 2nd CMDh meeting following submission
- MAH will be informed by CMDh-Secretariate about
  - acceptance
  - Worksharing MRP-Number

C. Safety, Efficacy, PharmVigil – (1)

C.I.3 Implementation of change(s) requested by the EMEA/ National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH		1, 2	IB
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH			II

… first experiences Worksharing

- some MAH have indicated, that they are not able to run worksharing due to their internal structure
- preference to run worksharing in parallel, despite grouping would be possible (new manufacturer)
- so far no worksharing on grouped application
- 1st Worksharing (DE) was sucessfully run as a 30-Day procedure (pharmacovigilance) – MAH is happy and back with the next one (SSRI-recommendations) …


Federal Institute for Drugs
and Medical Devices (BfArM)
... many thanks
for your kind attention
Questions ?
The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health