Variation Update

14. DGRA Jahreskongress

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Content

- Experience with grouping and worksharing
- Revised Variation Regulation
- Further steps

Grouping experiences

- many questions concerning possible groupings after implementation
- procedure was only used hesitantly in the beginning but grouped applications are regularly increasing
- number of applications could be significantly reduced
- regular update of list of possible grouped applications by CMDh

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

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

Doc. Ref: CMDh/173/2010/Rev4
June 2011

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

- All minor notifications of type IA and type IA_{IN} may be grouped in one application without any relation to each other, if the group includes only type IA and type IA_{IN}.

[1] Purely editorial changes can automatically be included as part of another variation to the same part of the dossier, provided that they do not change the actual content of the dossier and therefore the meaning of any text. This also includes editorial changes to the SmPC (see also Q/A 3.16).

Number of variations per group (1)

Safety and efficacy changes:

- The scope of a variation derives from a specific dataset affecting specific section(s) of the SmPC
- The scope can derive from more than one dataset in case the SmPC changes concern the same section(s) and paragraph(s) of the SmPC and are considered to relate to a similar issue

Number of variations per group (2)

Quality changes:

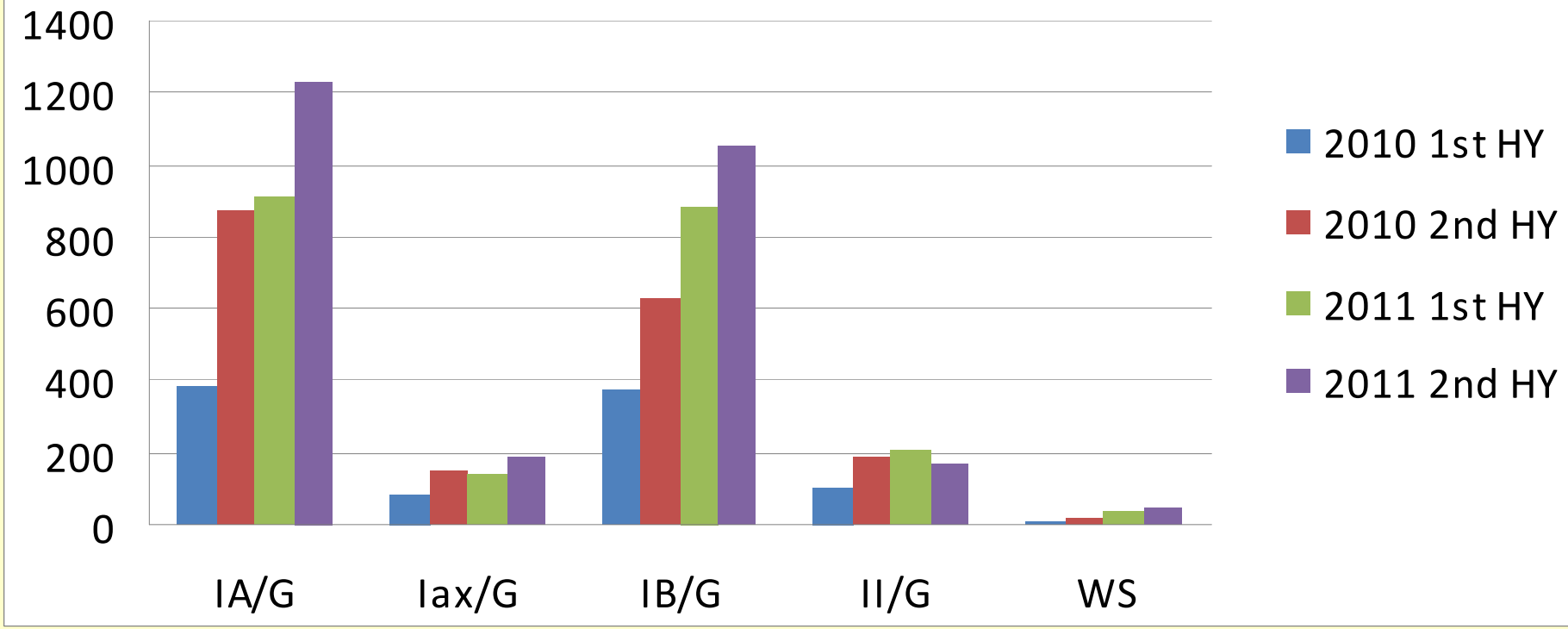
- The scope of a variation is defined at the level of the individual indents of each general scope in the classification guideline

Other changes:

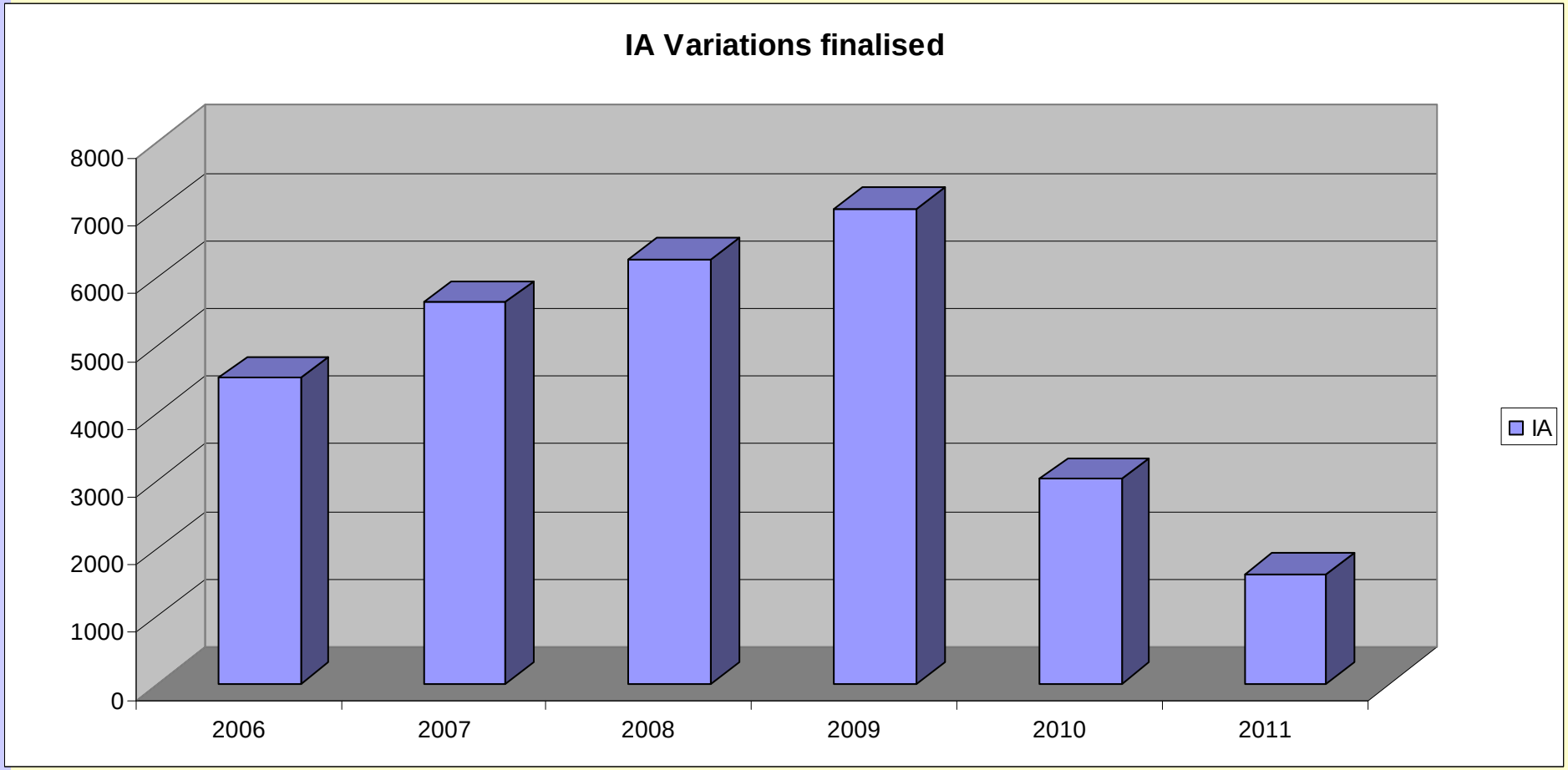
- Editorial or other minor changes can be included within the scope of another planned variation and do not need a separate variation application

Grouped Variations/Work sharing by type and creation date

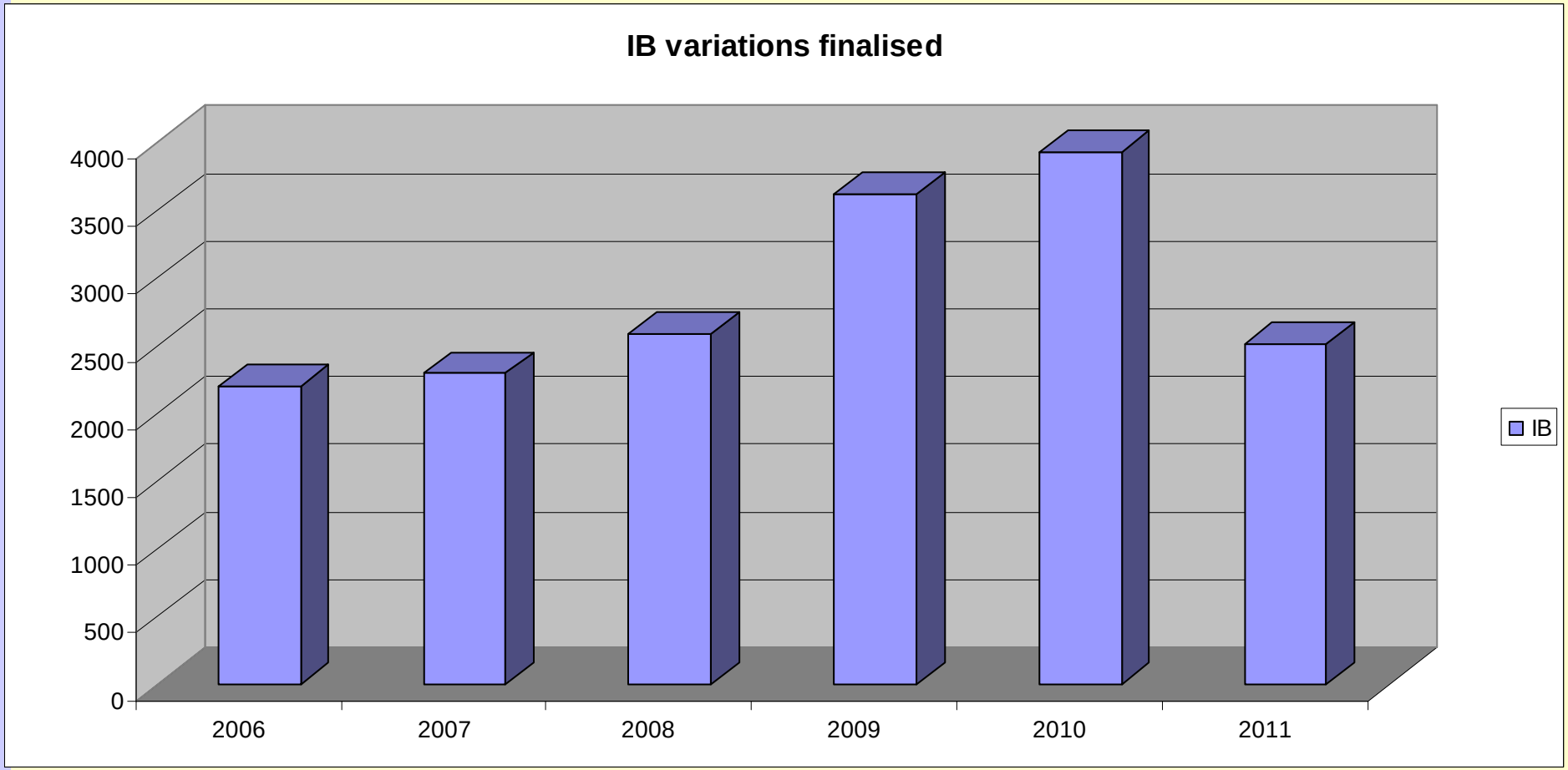
(source:CTS; status 07.02.2012)



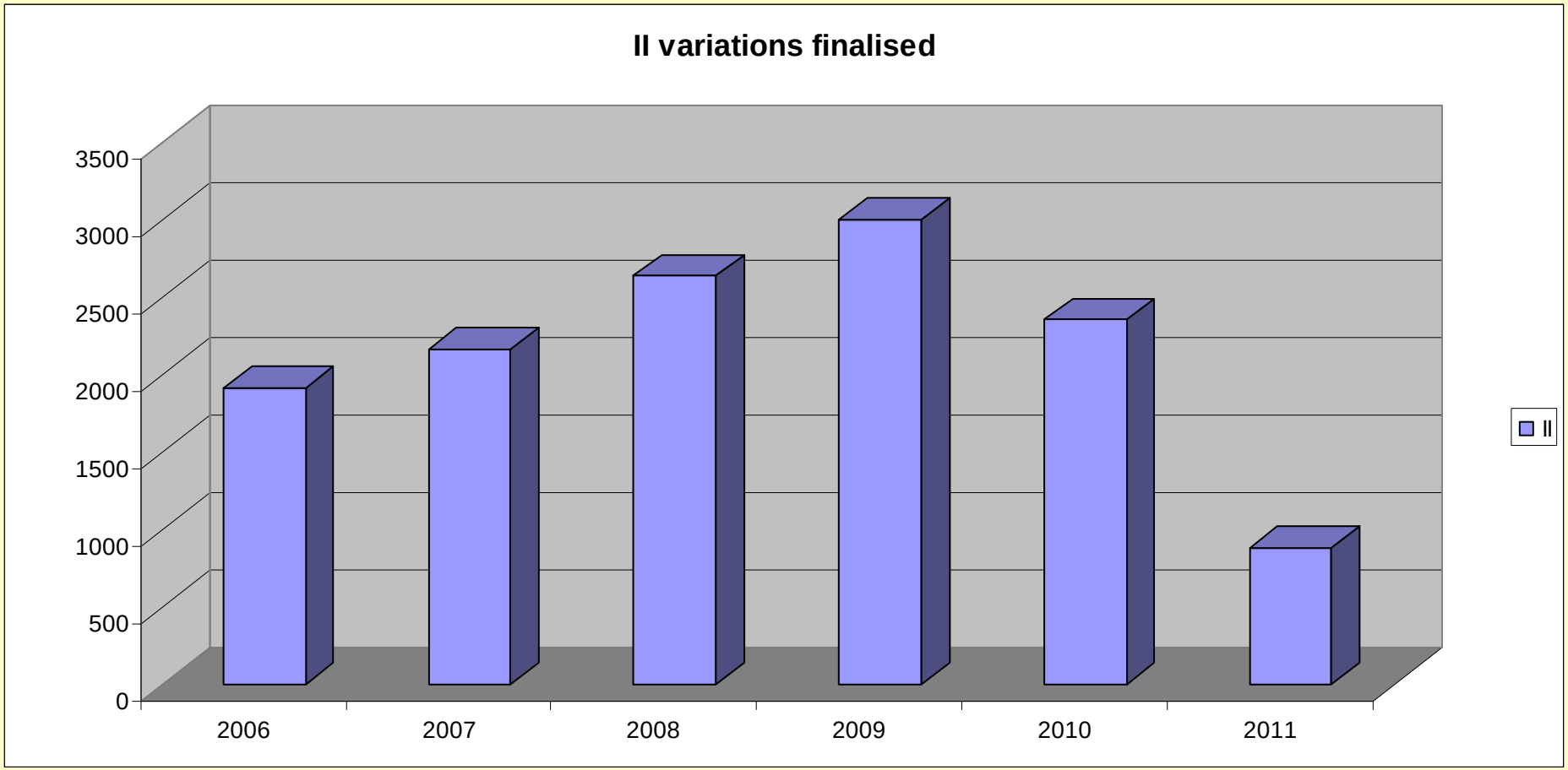
Type IA Variations finalised (source CMDh)



Type IB Variations finalised (source CMDh)



Type II variations finalised – source CMDh



Worksharing experiences (1)

- So far more than 100 Worksharing procedures for only MRP/DCPs accepted by CMDh
- 13 mixed worksharing procedures with „CAP“ and „NAP“ with EMA as reference authority
- ca. 60 worksharing procedures positively finalized
- 2 worksharing applications were rejected by CMDh as only one type IA change or, resp., 1 MA was concerned
  ⇨ advice to use grouped application per RMS

Worksharing experiences (2)

Content of the procedures different:

- Adaptation to PhVWP recommendations
- Significant update of SmPC due to new pharmacovigilance / clinical data
- Change in manufacturing sites (IB)
- Other changes of the quality dossier

Worksharing - examples

October

B.I.a.2.c (G)

B.I.b.2.d

C.I.4.a (G)

C.I.4.a (G)

C.I.4.a

November

B.I.a.2.c

December

C.I.4

C.I.3

C.I.4

B.I.b.2.e

January

B.II.e.1.b.1

C.I.8.a

C.I.4

C.I.2.a

February

C.I.8.a

B.II.b.1.f

B.II.b.3.c

B.II.d.2.d

B.I.a.2.c

C.I.z

C.I.4

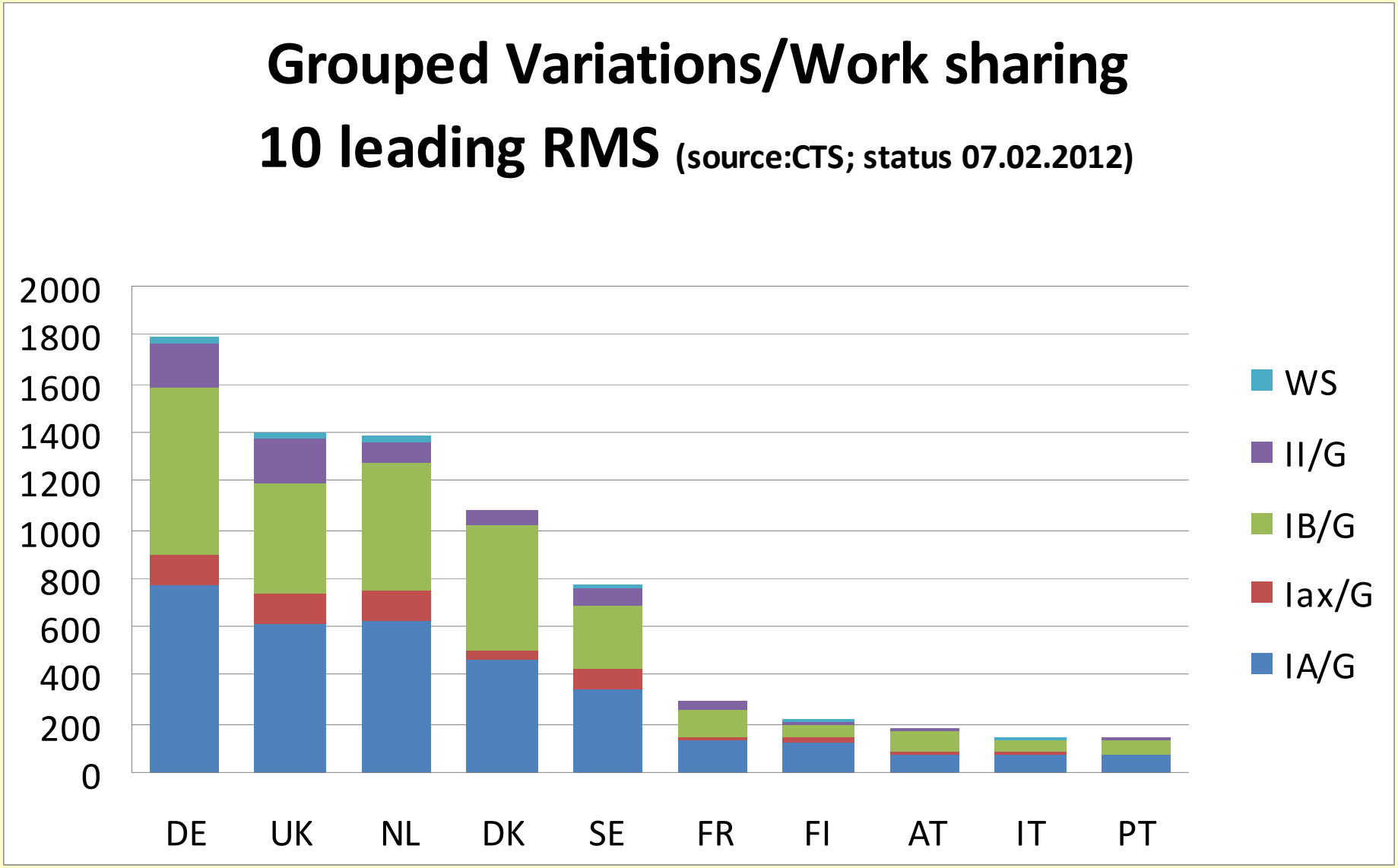
C.I.4 & C.I.3.a

C.I.4

15

Grouped Variations/Work sharing

10 leading RMS (source:CTS; status 07.02.2012)



Worksharing experiences (3)

New approach for procedures with only one RMS:

- All products concerned have the same RMS
- The RMS agrees to be the reference authority in the worksharing procedure and issues the number
- The RMS informs the CMDh secretariat about the new worksharing

⇨ Several simplifications are under discussion

⇨ Regulation has to be observed!!!

BPG Chapter 7:
Worksharing of MR/DC procedures with the same RMS

In case the intended worksharing procedure only includes MR/DC procedures with the same RMS and the MAH proposes the RMS to be the preferred reference authority, the pre-submission information should be directly submitted to the RMS. The RMS takes the decision whether or not the intended submission can be agreed as a worksharing procedure.

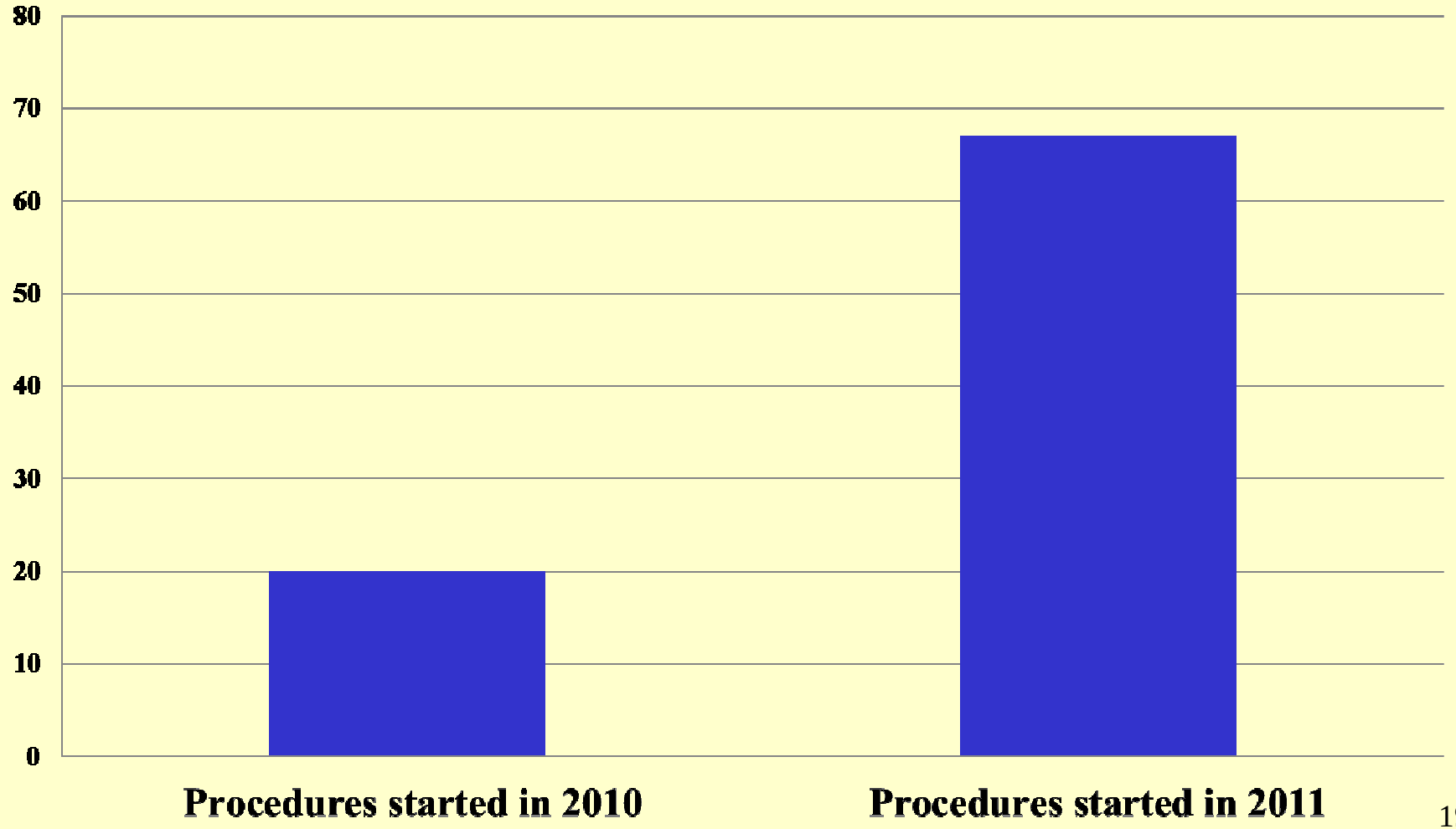
If not agreed upon, the RMS requests that the MAH submits its pre-submission information together with the reasons for non-acceptance by the RMS to CMDh as described above under the paragraph “Worksharing of MR/DC procedures with more than one RMS”. The procedure described in that paragraph will then be followed. The RMS of the procedures involved in the worksharing procedure will remain the proposed Reference Authority. The MAH should then wait to submit the worksharing application until they have received confirmation of the CMDh whether the worksharing request has been accepted.

If the worksharing request is agreed upon, the RMS communicates this to the MAH, provides the procedure number to the MAH and indicates that they may then submit the variation to RMS and all CMSs.

The RMS will forward the pre-submission information together with the procedure number on the agreed worksharing request to the CMDh Secretariat for inclusion in the agenda for information of the next CMDh meeting and will inform the CMDh Secretariat of their agreement with the proposal.

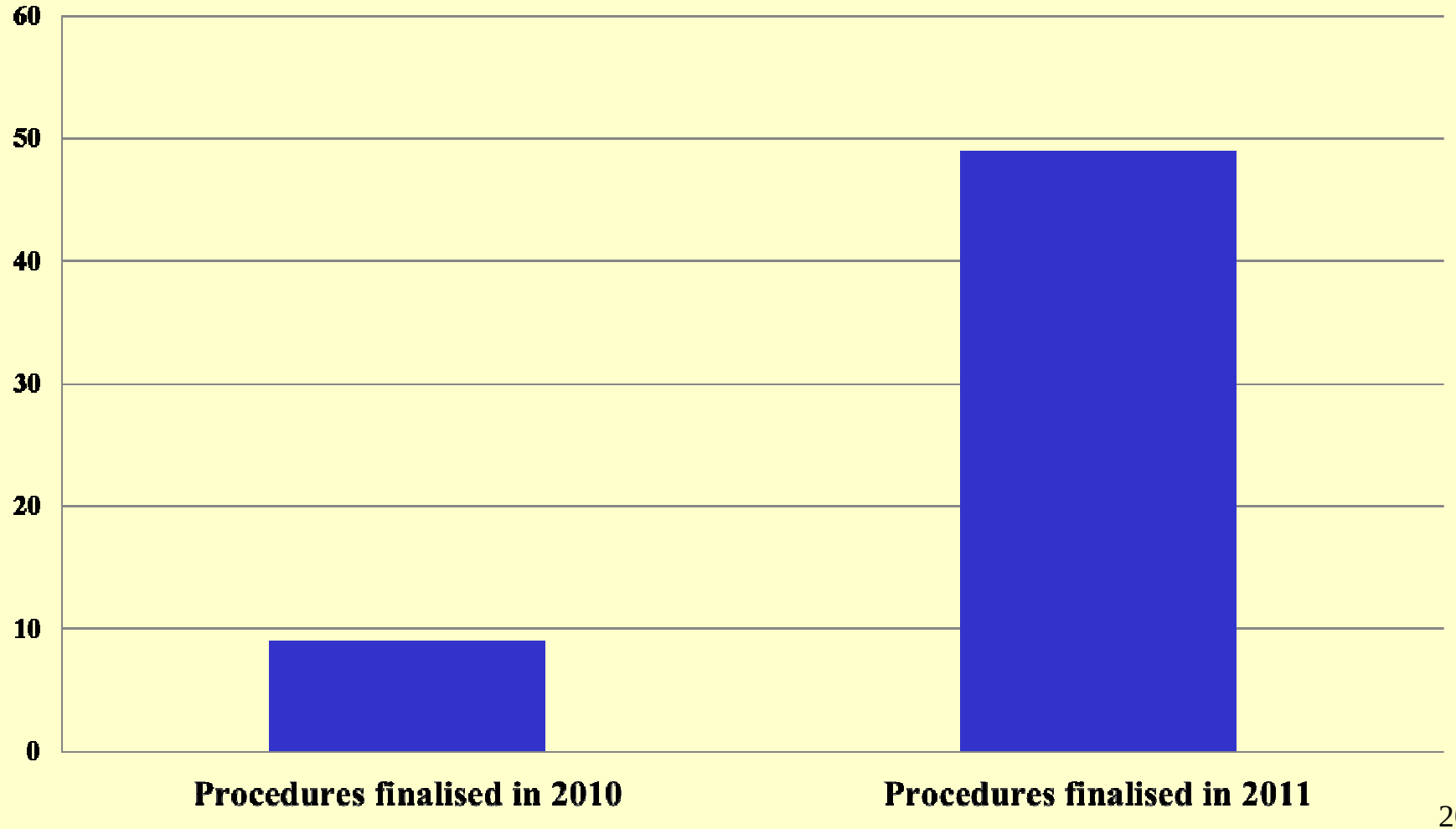
Implementation of variation regulation
1st January to 31st December 2011

Worksharing Procedures Started (2010/2011)



Implementation of variation regulation
1st January to 31st December 2011

Worksharing Procedures Finalised (2010/2011)



Revised Variation Regulation

Scrutiny-Procedure already started!!

Recitals (1)

1) scope of 1234/2008 has to be extended
2) consider Regulation (EU) 1235/2010
3) purely national licences should be processed acc. to same principles as DCP/MRP
   -> grouping adapted to characteristics of purely national licences
4) purely nationals may participate in worksharing – harmonised outcome has to be kept

Recitals (2)

5) grouping is possible –> complex groupings may have an extended timetable

6) worksharing is possible for combination of CP, MRP/DCP and purely nationals

7) Procedure for human influenza vaccines is streamlined -> procedures may start without clinical + stability data

Recitals (3)

8) CP variations are terminated when EMA refuses acceptance
-> Comm. Dec. not required when variation does not amend MA decision

9) EMA, not EC, is responsible for USR for CP

10) Critical changes for CP implemented promptly, others within 12 months

11) special changes may be implemented before MA is amended

Article 2, par. 8

"*Urgent safety restriction' means an interim change in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product.*"

- ⇨ no longer restricted to product information
- ⇨ now also foreseen for quality problems (GMP)

Article 2, par. 9

- Definition of purely national MAs:

  „Purely national MA“ means any MA granted by a MS in accordance with the acquís outside MRP or DCP and that has not been subject to a complete harmonisation following a referral procedure.”

Article 4, par. 1

- „Interested parties“ deleted:

  The Commission shall, after consulting the Member States and the Agency, draw up guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of this Regulation, and on the documentation to be submitted pursuant to those procedures.

Article 5, par. 1 (1)

- Procedure changed:

  Prior to the submission of a variation whose classification is not provided for in this Regulation, a holder may request a recommendation on the classification of the variation as follows:

  - » **to the Agency**, where the variation refers to a marketing authorisation granted under Regulation (EC) No 726/2004,
  - » **to the competent authority of the Member State concerned**, where the variation refers to a purely national marketing authorisation,
  - » **to the competent authority of the reference Member State**, in the other cases.

Article 5, par. 1 (2)

- The recommendation referred to in the first subparagraph shall be consistent with the guidelines referred to in Article 4(1). It shall be delivered within **45 days** following receipt of the request and sent to the holder, the Agency, and the coordination group referred to in Article 31 of Directive 2001/82/EC or in Article 27 of Directive 2001/83/EC.
- The 45-day period referred to in the second subparagraph **may be extended by 25 days** where the relevant authority deems it **necessary to consult with the coordination group** ."

Article 5, par. 1a

- Prior to the examination of a variation whose classification is not provided for in this Regulation, **a competent authority of a Member State may request a recommendation on the classification of the variation to the coordination group**.
- The recommendation referred to in the first subparagraph shall be consistent with the guidelines referred to in Article 4(1). **It shall be delivered within 45 days following receipt of the request** and sent to the holder, the Agency, and the competent authorities of all Member States."

Article 7 (c) and Article 10 (2)

- Extended timetable for complex groupings:

  "*The competent authority of the reference Member State may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or extend it to 90 days for variations listed in Part 1 of Annex V* ***or for grouping of variations in accordance with Article 7(2)(c)***."

Article 12, par. 3, 4, 5, 6

3. The competent authority of the reference Member State shall assess the application submitted. **Where deemed necessary**, the competent authority of the **reference Member State may request additional data** to the holder in order to complete its assessment.
4. The competent authority shall prepare a decision and an **assessment report within 45 days** from the receipt of a valid application.

   The 45–day period referred to in the first subparagraph shall be suspended from the moment when the additional data referred to in paragraph 3 is requested until the data is submitted.
5. Within 12 days from the receipt of the decision and the assessment report of the competent authority of the reference Member State, the relevant authorities shall adopt a decision accordingly and inform the competent authority of the reference Member State and the holder thereof.“
6. deleted

Article 12

New proposal reflects:

1) need to maintain the overall timetable to ensure timely availability
2) additional flexibility how to spend assessment time
3) streamline decision-making process and avoid two decisions on same application

Chapter IIa – purely national MA

- Introduced after Article 13
- Subpar. a-c for IA, IB and type II identical to MRP/DCP
- New subpar. d for **horizontal grouping** of **purely national MAs**:

  where the same variation(s) to the terms of **one or more marketing authorisations** owned by the same holder are submitted at the same time to the same competent authority and they are not covered under subparagraphs (a) or (b), a single submission may cover all such variations provided that the competent authority agrees to such single submission.

Chapter IIa – purely national MA

Proposal reflects the need:

1) to keep similar procedures for purely nationals and MRP/DCP
2) some adjustments such as no need for consultation of other MS and no need for preparing assessment reports

Article 17

Working relations between EMA and EC when closing procedures:

(a) it shall inform the **holder** of the outcome of the assessment;

(b) where the variation is rejected, it shall inform the **holder** of the grounds for the rejection;

(c) where the outcome of the assessment is favourable and the variation **affects the terms of the Commission decision granting** the marketing authorisation, the **Agency shall transmit to the Commission its opinion and the grounds for its opinion** ...

Article 20, par. 1 (b)

- **Purely national MAs may be combined with MRP/DCP**:

  for purely national marketing authorisations referred to in Chapter IIa, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in Article 13d(2) (b) or (c) that does not contain any extension relates to several marketing authorisations owned by the same holder;

Article 20, par. 1 (c) (1)

- **Only purely nationals, licenced in several MS**:

  for purely national marketing authorisations referred to in Chapter IIa, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in Article 13d(2) (b) or (c) that does not contain any extension relates to one marketing authorisation that is owned by the same holder in more than one Member State

Article 20, par. 1 (2)

- All procedures can be mixed:

  Variations covered under (a), (b), or (c) may be subject to the same worksharing procedure.

Article 23 and 23a

- Hint on paediatric regulation was deleted and replaced by Article 23a:

  *The **statement indicating compliance** with the agreed completed paediatric investigation plan provided for under Article 28(3) of Regulation (EC) No 1901/2006 shall be **included within the technical dossier of the marketing authorisation**.*

  *The relevant authority shall provide the holder with a **confirmation that the statement is included in the technical dossier within 30 days** after the relevant assessment has been concluded.*

Article 23, par. 1a:

Amendments to the decision granting the marketing authorisation resulting from the procedures laid down in Chapter III shall be made:

(a) within two months following receipt of the information referred to in Article 17(1)(c) for the following variations:

(i) variations related to the addition of a new therapeutic indication or to the modification of an existing one;

…

Art. 23, par 1(b)

(b) within twelve months following receipt of the information referred to in Article 17(1)(c) in the other cases.

Article 24a

Application of national provisions on variations to purely national marketing authorisations

Member States that, in accordance with Article 23b(4) of Directive 2001/83, may continue to apply their national provisions on variations to certain purely national marketing authorisations are listed in Annex VI to this Regulation."

Entry into force

1. This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.
2. It shall apply from [90 days following that of its publication].

   However, points (10), (15), (18)(a) and (c), (21), (22) and (23) of Article 1 shall apply from [12 months following publication in the Official Journal of the European Union]

(= chapter IIA, Article 20, Article 23 (1)+(2), title of Annex III (grouping), Annex VI)

Further steps

Further steps

- Update of classification guideline – further public consultation procedure
- Update of procedural guideline – as soon as scrutiny procedure is closed?
- CMDh already prepares updates of necessary guidance documents
- National implementation of the Variation Regulation has to be prepared internally in BfArM

Thank you for your attention –
any questions?

List of Abbreviations

- AMG = Arzneimittelgesetz (German Drug Law)
- BPG = Best Practice Guide
- CCDS = Company Core Data Sheet
- CMD = Coordination Group for MRP and DCP
- CMS = Concerned Member State(s)
- CAP = Centralized Procedure
- CR = Commission Regulation
- DCP = Decentralized Procedure
- MA = Marketing Authorisation
- MAH = Marketing Authorisation Holder
- MRP = Mutual Recognition Procedure
- NAP = Nationally authorised product (MRP/DCP)
- NCA = National Competent Authority
- PAG = Post authorisation guidance (EMA)
- PI = Product Information
- PIL = Patient Information Leaflet
- RMS = Reference Member State
- SmPC = Summary of Product Characteristics