EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The role of the European Medicines Agency in the new Variations Regulation

Regulatory Affairs
Regulatory, Procedural and Committee Support

Sonia Ribeiro
22 January 2010

Agenda

Aim of new Variations Regulation

Main features & scope

The role of the Agency:

- Prior to implementation
- After implementation

Main Challenges

- Article 5 recommendations
- Grouping
- Worksharing

Questions

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Variations Regulation (EC) 1234/2008

Aim of new Variations Regulation

- ✓ Simpler, Clearer, More flexible legal framework
- ✓ Reduce administrative burden
- ✓ Adapt to ICH concepts
- ✓ Further harmonise handling of variations in EU

Same level of public and animal health protection

The revision project

Review of
the **legal basis** of
the Variations Reg.
(Dir 2001/83/EC, 2001/82/EC, 726/2004)

⇨ Co-decision Procedure (Dir. 2009/53)

Transposition by 20 Jan.2011

Review of
the **content** of
the Variations Reg.
(Reg 1084&1085/2003)

⇨ Comitology procedure (Reg.1234/08)

Applies from 1st January 2010

Main features & scope

- Type IA 'Do and tell' *(annual reporting)*
- Type IB by default
- Grouping *(facilitate review & reduce administrative burden)*
- Worksharing *(avoid duplication of work)*
- CMD referrals *(increase cooperation between MSs)*
- Implementation of variations by MAH

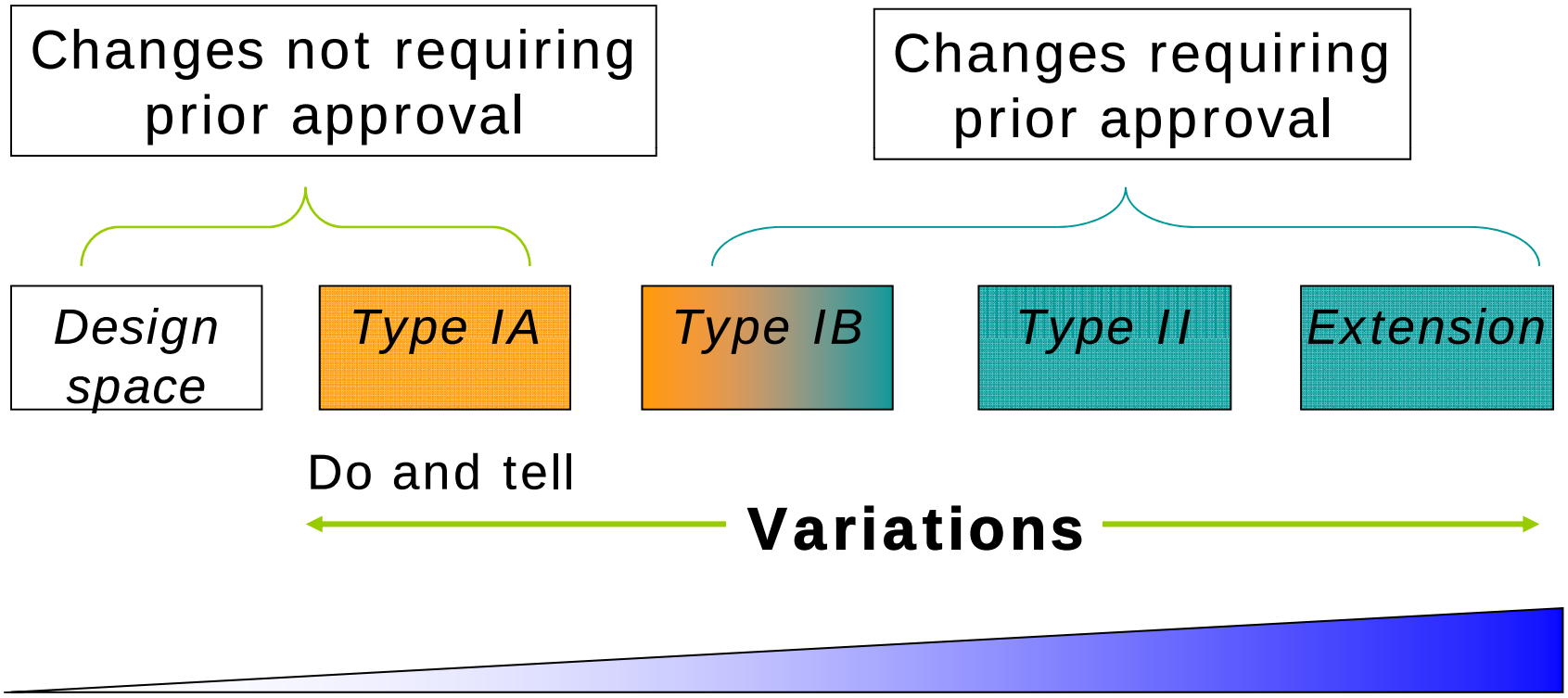
Main features & scope

Classification of variations depending on **level of risk** to public or animal health &

Impact on the quality, safety and efficacy of medicinal product concerned

- Applies to:
  - Medicinal products authorised via **MRP, DCP**
  - Following a **CHMP referral** (full harmonisation)
  - Medicinal products authorised via **CP**

Types of Variations



Evaluation Procedure adapted to the level of risk

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The role of the Agency

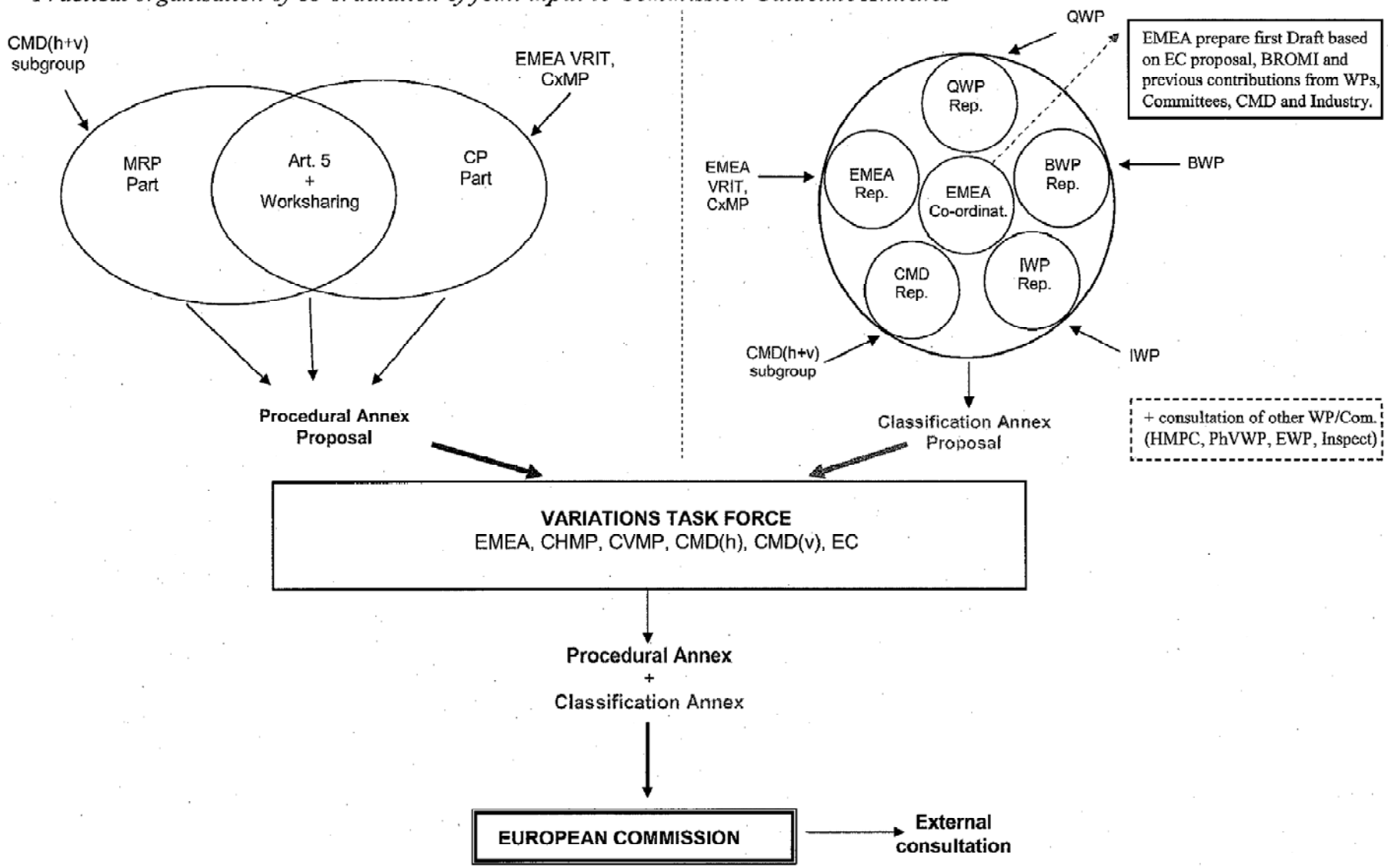
Prior to implementation

- EC Guidelines: Procedural + Classification

The Agency to co-ordinate joint input of CMD(h), CMD(v), CHMP, CVMP, EMA

EU Variations Task Force

Practical organisation of co-ordination of joint input to Commission Guideline Annexes



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

Prior to implementation

At EU level

- Co-ordinating role in EU Variation Task Force
- Participation in CMD Variation Sub-group
  - Development of Variation application form
  - Agency's & MSs responsibilities in work-sharing, Art. 5
- eCTD Sub-group on Variations Regulation

Prior to implementation

At the Agency

Set up of VRIT (Variation Regulation Implementation Team)

- Handling of Type IA & annual reports
- Detailed classification & Art 5 recommendations
- Handling of Default Type IB & safeguard clause
- Grouping & Worksharing
- Decision Making Process
- Fees

Prior to implementation

- ✓ Update of existing SOPs & development of new SOPs
- ✓ Update of templates (e.g. validation & AR templates, opinion templates, etc.)
- ✓ Dedicated section on the Agency website
- ✓ Revised rules on implementation of fees (grouping of variations and worksharing)
- ✓ Training of Staff (general and specific training at Sector level)

After implementation

- **Set up of ClAG (Classification Advisory Group)**

  - To advise on interpretation issues in relation to Classification Guideline

  - Central point for Article 5 requests

  - To make proposals for revision of Classification Guideline

  - Agency staff with scientific & regulatory experience (human or veterinary) quality (chemicals and biologicals), safety and efficacy

After implementation

- **Set up of G-WAG (Grouping and Worksharing Advisory Group)**

  - To advise on acceptability of proposed groupings and/or worksharings

  - To ensure a consistent approach within the Agency and provide internal support to PTLs

  - To keep track of accepted groupings and/or worksharing and to publish this information

  - Agency staff with scientific & regulatory experience (human or veterinary)

After implementation

- Continue to participate in CMD Variation Sub-group
- Ensure a harmonised approach with MSs on classification of variations, Article 5 recommendations, grouping and worksharing
- Organise a meeting of the EU VRIT Task Force
- Continue to provide further guidance on eCTD and variations

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Main challenges

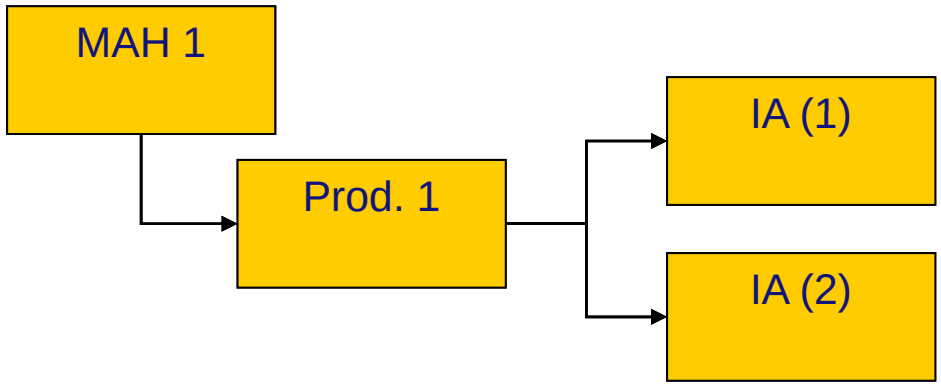
Article 5 recommendations

- MAH or MS to request CMD or the Agency for a recommendation on ‘unforeseen’ variation
- To be delivered within 45 days
- The Agency and CMD to ensure coherence of recommendations
- Possible discussion at CMD
- Publication of recommendations

Revision of Classification Guideline & Annex II

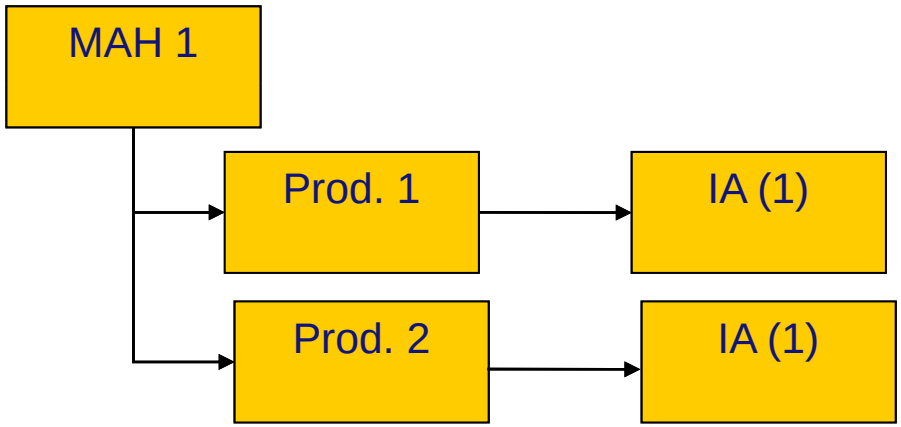
Grouping of Type IAs

>1 type IA or IA_{IN} affecting one MA



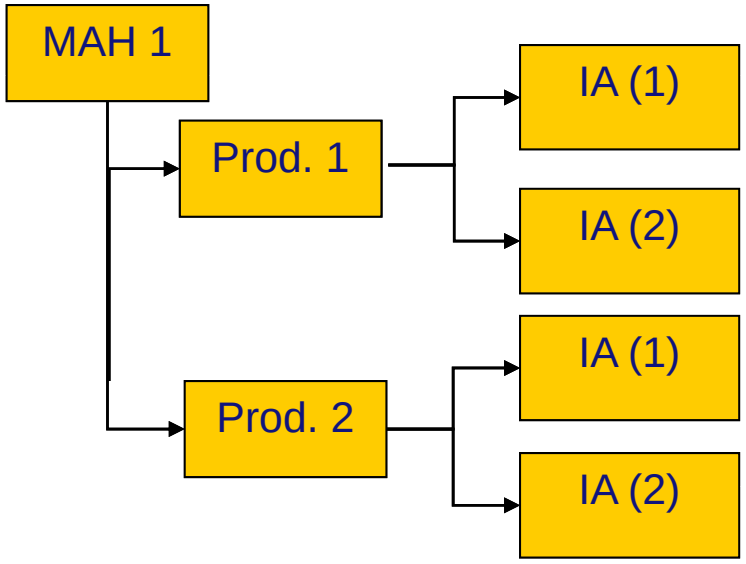
Grouping of Type IAs

1 type IA or IA_{IN} affecting >1 MA from the same MAH



Grouping of Type IAs

>1 same type IA and/or IA_{IN} affecting >1 MA from the same MAH



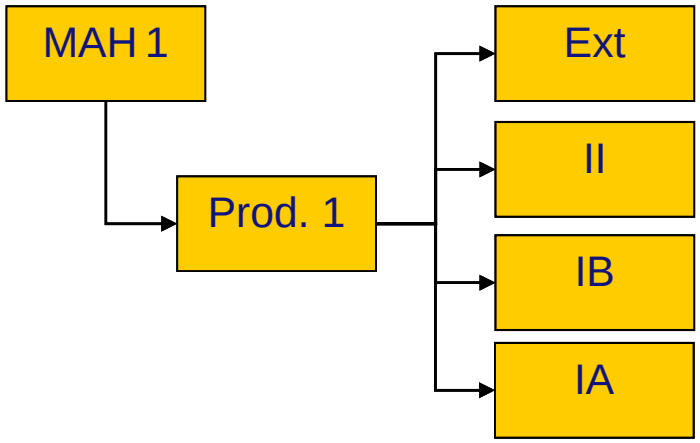
Grouping of Type IAs for several products

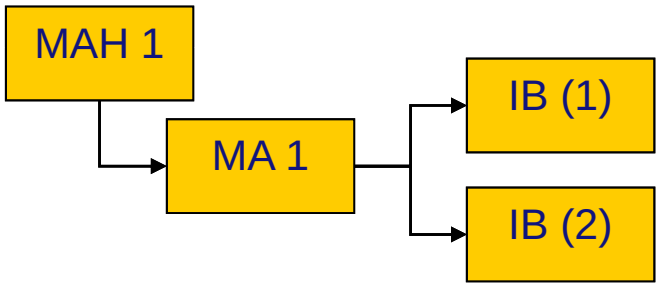
How to submit

- 1 application submission
  - 1 eCTD sequence per product
  - Common cover letter
  - Common application form
  - Individual revised product information (if applicable)
  - Individual supportive documentation covering all changes

Grouping of extensions, Type II, IB, IA

Article 7.2(b)





Grouping

14 cases for grouping listed in Annex III

- Extension + type II, IB, IA
- Changes to ASMF, VAMF or PMF
- Changes to manufacturing process
- Changes to the Pharmacovigilance system
- Changes further to PSUR, SO, FUM, class labelling
- …

Grouping

"1. One of the variations in the group is an extension of the marketing authorisation"

Extension application

+ Other clinical or non-clinical changes expected to be linked to the extension
+ Quality changes affecting the drug substance and/or drug product

Extension for a new pharmaceutical form for paediatric use

+ Type II for new paediatric indication in existing presentations

Extension for a new strength

+ Type II for change in the manufacturing process

Grouping

"2. One of the variations in the group is a major variation of type II; all other variations in the group are variations which are consequential to this major variation of type II"

Type II for substantial change to the manufacturing process of the active substance

+ Type IB for change more than 10 fold increase to the approved batch size

+ Type IA for addition of new specifications parameters to the specification with the correspond test method

Grouping – Other cases

- Grouping should always be justified
- Changes should be consequential and/or related i.e. **meaningful to be reviewed simultaneously**
- Quality, Nonclinical and Clinical cannot be mixed unless justified
- Quality variations to active substance cannot be mixed with finished product variations, unless consequential/ justified
- Grouping should not delay the submission and implementation of safety information

Grouping – Other cases

Quality example

- 1 Type IB - extension of a re-test period of the active substance
- 1 Type IB - change in the storage conditions of the active substance

Quality + administrative example

- 1 Type IB– extension of shelf life of finished product as packaged for sale
- 1 Type IA$_{IN}$ – change in name and/or address of manufacturer responsible for batch release
- 1 Type IA – change in ATC code

Grouping – Other cases

Generic / hybrid / biosimilar

- Grouping of type IB or II for each change applied to the reference product

Change of indication + legal status

- 1 Type II to change the indication
- 1 Type II to switch to OTC

Several drug-drug interaction studies

- 1 Type II variation with DDI study with rifampicin
- 1 Type II variation with DDI study with oral contraceptive

Grouping – Not acceptable

2 different indications

- Renal cell carcinoma + non-small cell lung cancer

Not consequential or meaningful

- 1 Type II with interaction study results
- 1 Type II with PK study results in renal impairment

Broad "CCDS" update

- 1 Type II to update posology information in section 4.2
- 1 Type II to update section 4.9 with overdose case
- 1 Type II to update section 5.1 with new pharmacodynamic property data

Grouping of extensions, Type II, IB, IA

How to submit

- 1 application submission as 1 eCTD sequence including:

  - 1 cover letter

  - 1 variation application form (+ 1 extension application form, if applicable)

  - Revised product information (if applicable)

  - Integrated package/supportive documentation covering all changes

Grouping

How to handle:

NOT a “all or nothing approach” BUT partial acceptance

- **1** Opinion/Notification

  - listing variations which are approvable and not approvable (unless withdrawn)

  - If withdrawn: Opinion/Notification reflects final outcome i.e. ‘highest’ approvable variation in group

  - X + II + IB ➔ X withdrawn ➔ **II** opinion & decision making procedure

Worksharing

Article 20: (...) minor variation of **type IB**, a major of **type II** or a **group** of variations ** (...) relates to several marketing authorisations owned by the same holder (...)

** Note that EXTENSIONS are excluded

i.e. **SAME** variation or group of variations

MORE than one product

ONE MAH

OPTIONAL procedure (not mandatory)

Who takes the lead?

The Reference Authority

i.e. the **Agency** when at LEAST ONE of the MAs is a centrally authorised product (CAP)

ONE MAH can submit a variation applicable to **several (different) MAs**, which can be

- Mix of CAPs
- At least one CAP and MRP/DCP products

Rules

1) Same change(s) applying to different MAs; **same dataset**; no need for any additional product specific assessment => Worksharing **OK**

2) Same change(s) applying to different MAs; **common dataset** and common core assessment, but with limited need to review impact on individual products => Worksharing **OK**

3) Same change(s) applying to different MAs; **separate datasets** for each individual product which require separate assessments => **NO** Worksharing

Clinical/ PhV Examples

- Changes to DDPS
- Implementation of class labelling
- Changes to multiple generic MAs containing the same active substance
- Changes to single-substance MAs and fixed-combination MAs containing the same active substance
- Proposal for combination use, affecting both MAs
- PSUR outcome implementation for MAs with same active substance

Dossier

1 integrated submission package covering all variations for all products:

- one common cover letter
- one EU variation application form
- separate supportive documentation for each product

Submission per MA (eCTD, NeeS, paper)

Dossier requirements

- Submission at the same time to the Agency, Rapporteur WS and all MSs where the products concerned are authorised

- For the number of copies of the application the Agency's post-authorisation dossier requirements can be followed for CAPs and NAPs

Appointment of Rapporteur

- Possible rapporteurs:
  - Rapporteurs for CAPs or
  - CHMP members representing RMS for MRP/DCP

- Appointment is based on expression of interest and statistical rota system

- CHMP chair to appoint & formal adoption by CHMP

Validation

- Validation by the Agency
- Contact points for referrals to check Annex B
- Coordinating PTL to send an e-mail to MSs with deadline for validation & planned start of procedure
- MSs can inform the Agency in case of **non-receipt of the application and/or non-payment of the fees** only when this requires non-validation of the application => do **NOT** start WS procedure for all MAs until this is resolved

Evaluation

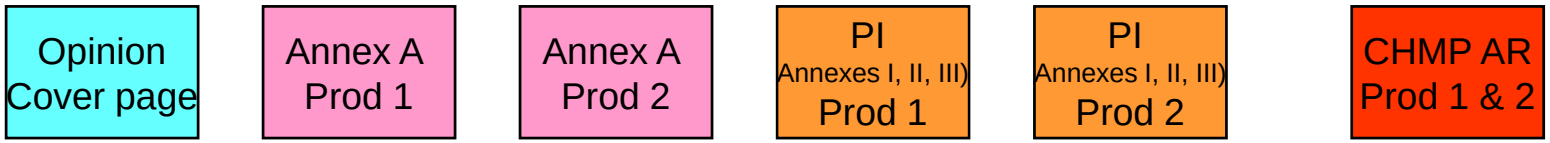
- Timetable:
  - **60 days** (default) for Type IB or Type II WS procedures, or
  - 90 days for variations listed in Annex V (extension of indication), or
  - 30 days or shorter, if urgent **and** for variations exact implemention of agreed SPC/PL wording by CHMP with no additional data
- No direct involvement of NCAs or CMD(h) => **input via CHMP members of their MS**
- All CHMP members expected to comment and the concerned CHMP member to highlight minor product specific issues

Opinion

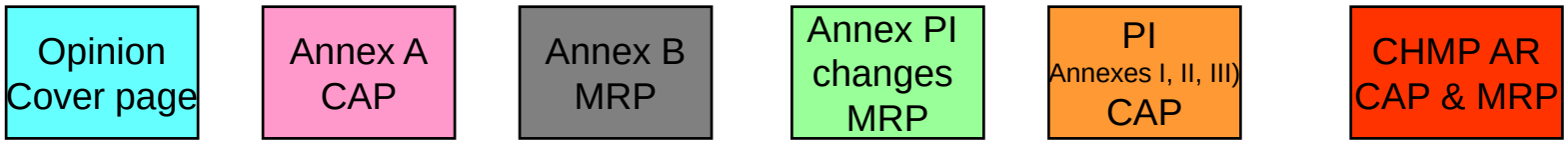
- 1 opinion:
  - List of favorable & unfavorable variations as part of a group or a specific product
- 1 CHMP assessment report
- Annexes of the opinion:
  - Annex A for each CAP
  - Annex B (list of NAPs)
  - Annexes I, II and III for each CAP (if affected)
  - Annex for the amendments to the PI of NAPs

Composition opinion

WS with 2 CAPs – no NAPs



WS with 1 CAP and 1 MRP



Post-opinion

- CHMP opinion to be sent to MAH, EC and **Member States**

- MSs to receive final opinion in order to implement the outcome at national level

Decision Making process

- CAPs: EC will update MA within 30 days (if necessary) => separate decision per MA
- NAPs: MSs to approve final opinion and update MA within 30 days, if necessary, unless a referral article 31 is initiated
- Implementation of variations:
  - Type IB (possible grouped with Type IA): implementation as of receipt of positive opinion
  - Type II: implementation as of 30 days after receipt of opinion

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Thank you!

Any questions?

Sonia Ribeiro
Regulatory Affairs Adviser

+44(0)20 7523 7231
Sonia.ribeiro@ema.europa.eu