New Variations Regulation 6 months experience

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1-2 June 2010, London, UK

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Agenda

- Aim of new Variations Regulation
- Main features & scope
- Experience with new provisions
- Points for discussion

Aim of New 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

Main Features & Scope

- Type IA ‘Do and tell’ *(annual reporting)*
- Type IB by default & Article 5
- Grouping *(facilitate review & reduce administrative burden)*
- Worksharing *(avoid duplication of work)*
- CMD referrals *(increase cooperation between MSs)*
- Implementation of variations by MAH

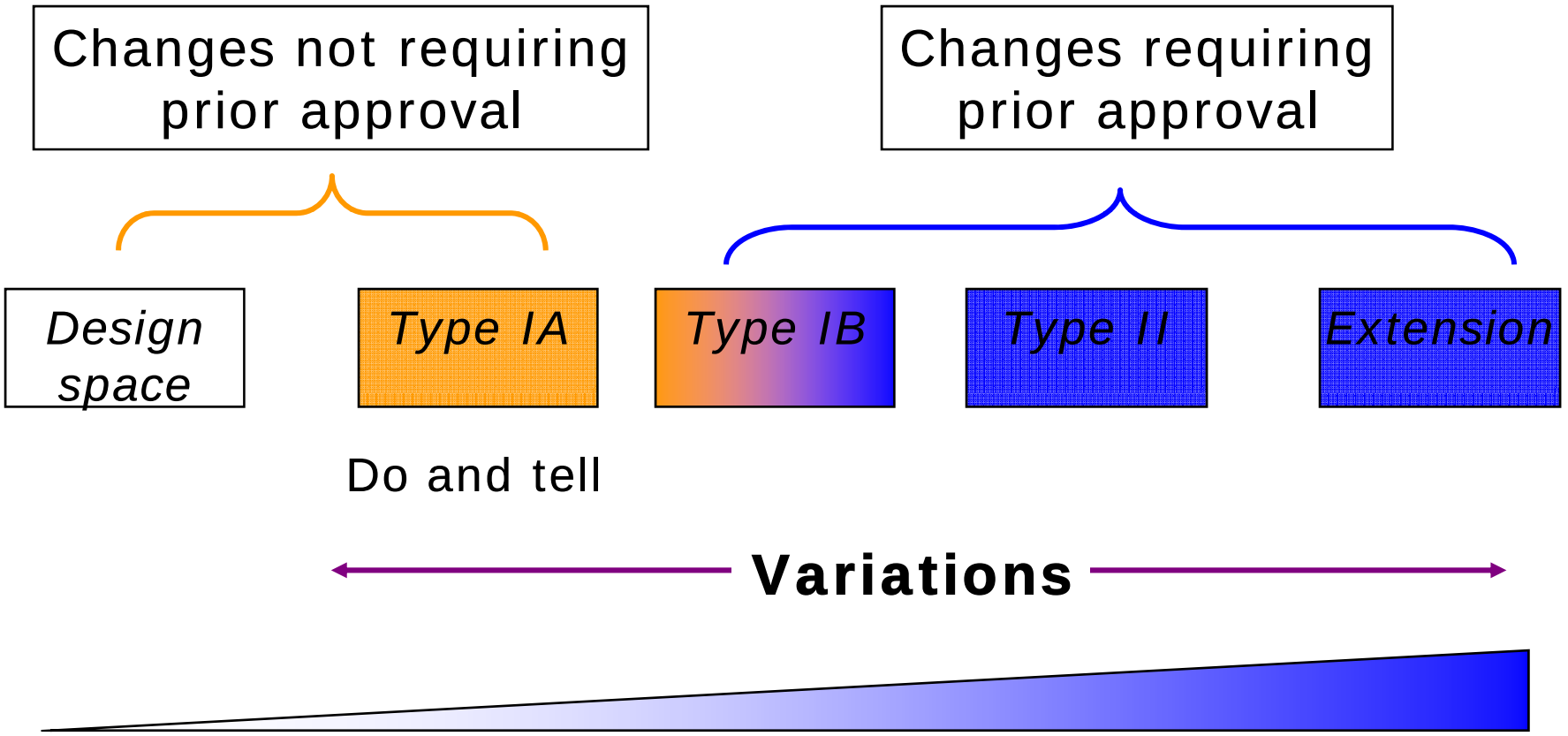
Main Features & Scope

- 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:

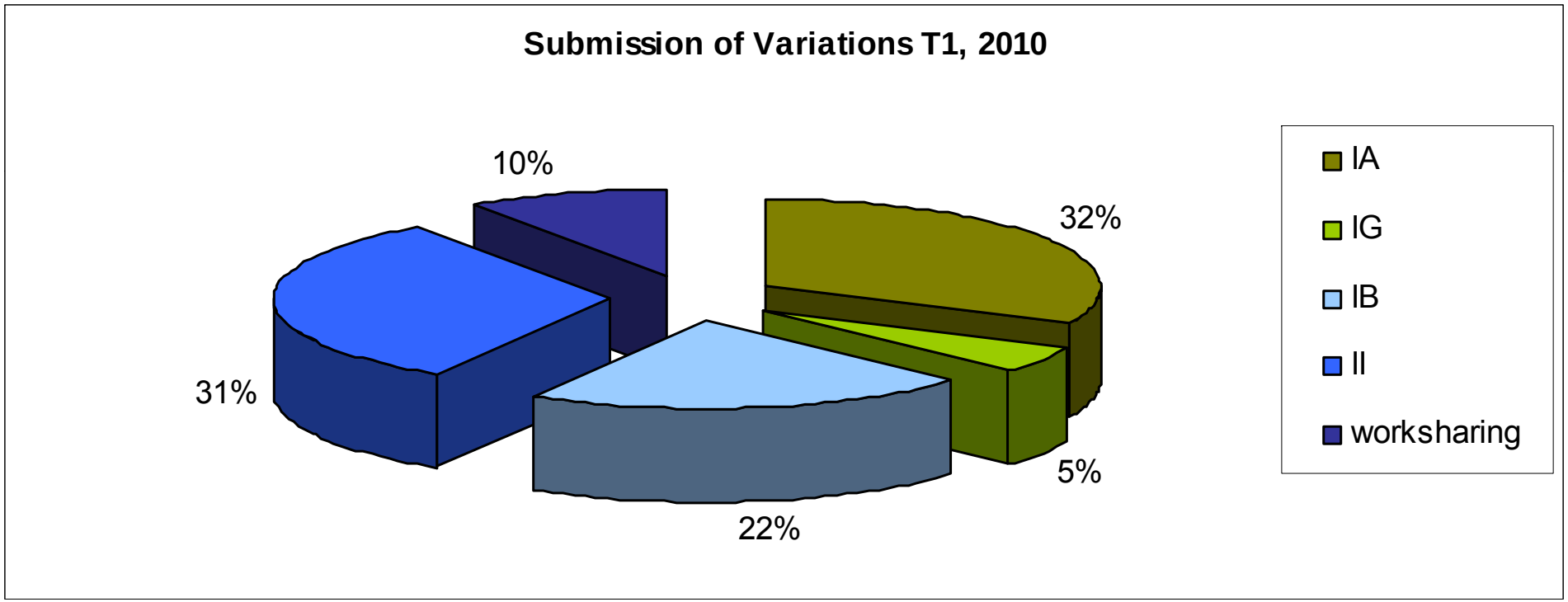
- Medicinal products authorised via **MRP, DCP**
- Following a **CHMP referral** (full harmonisation)
- Medicinal products authorised via **CP**

Types of Variations

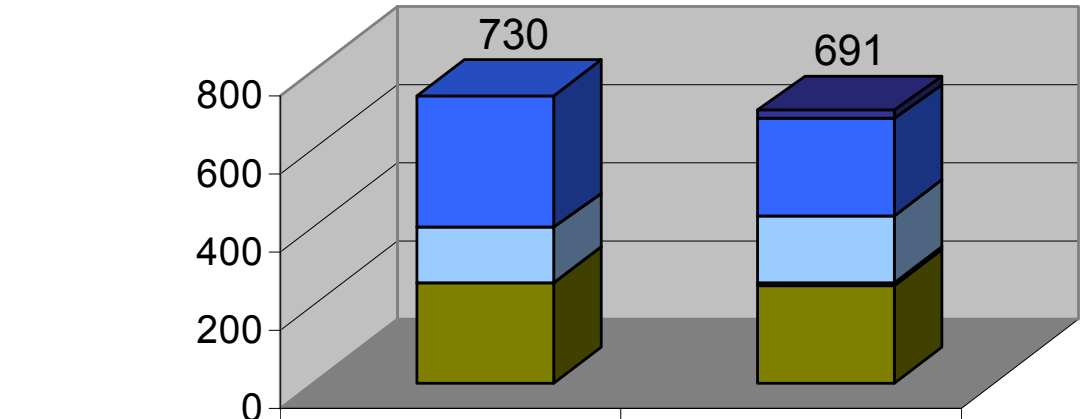


Evaluation Procedure adapted to the level of risk

Submission of Variations



Submission of Variations



	2009	2010
worksharing		21
II	336	245
IB	141	169
IG		7
IA	253	249

~ 22% Submissions in 2010 grouped

Type IA notifications

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

Type IA

IA: Agency notified <u>within 12 months</u> following implementation

IA_{IN}: Agency notified <u>immediately*</u> after implementation

**Changes for which <u>continuous supervision</u> is needed*

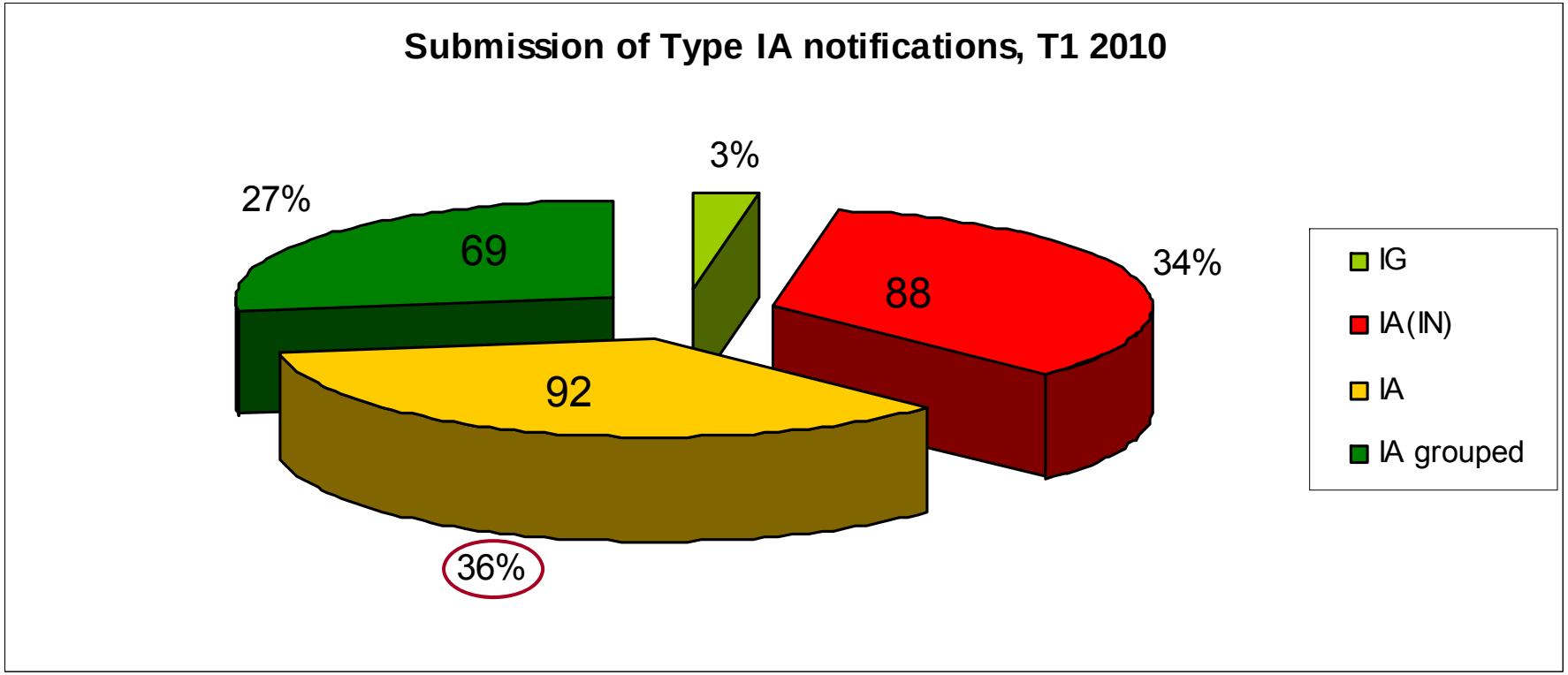
Type IA notifications

Implementation

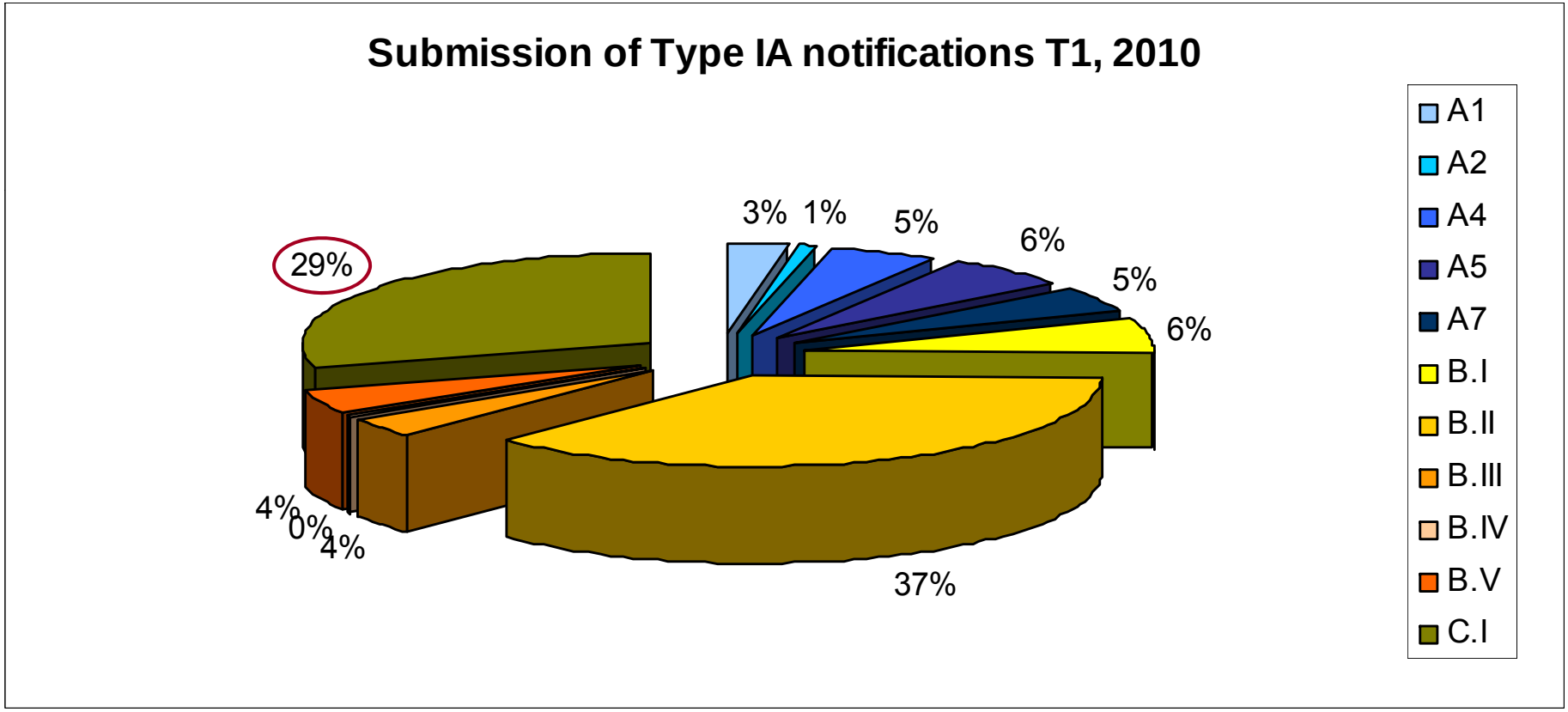
- Quality change - change in the Company's quality system*
- PhV change - when Company makes the change in the DDPS
- Product information (PI) - when revised PI is approved

* *This allows Companies to manufacture conformance batches and generate data necessary before immediate notification*

Type IA notifications



Type IA notifications



Type IA notifications

- Number of submissions for Type IA in 2010 ≈ 2009 (256 vs 253)
- Total number of notifications increased in 2010 by ~ 60%
- IG notifications contain an average of 5.6 products
- Examples of IG notifications:
  - A.7, B.II.d.1.c, B.III.1.a.2, C.I.9

Type IA notifications

- MAHs advised to submit Type IA variations as part of the **Annual Report**, except for:

  - Type IA_{IN} – To be submitted immediately!

  - Type IA affecting the PI - To be submitted with the next variation affecting the PI

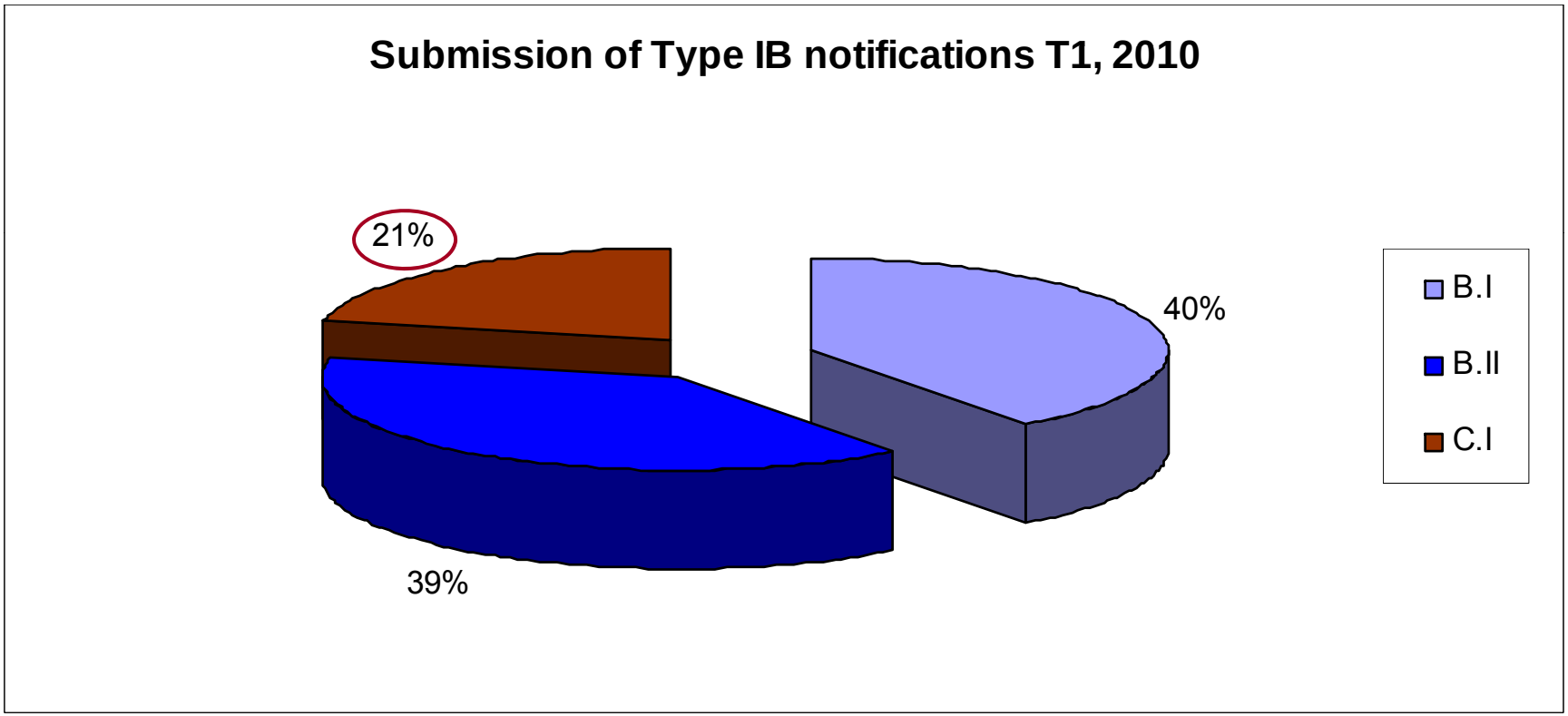
- Further reduce overall number of variations submissions
- Better use of Competent Authorities resources

Type IA notifications

- Possible to group, Art. 7.2(a):
  - **>1** type IA or IA_{IN} affecting **one MA**
  - **1** type IA or IA_{IN} affecting **>1 MA**
  - **>1 same** type IA and/or IA_{IN} affecting **>1 MA**

- All Type IAs listed in the guideline
- Quality or S/E, PhV changes
- Conditions to fulfil & documentation to be provided

Type IB notifications



Type IB notifications

- Number of submissions in 2010, 20% > in 2009 (141 vs 169)
- Total number of notifications increased in 2010 by ~25%
- Number of Type II variations 30 days ≈ Type IB notifications C.I
- ~ 16% Type IB ‘unforeseen’

Article 5 recommendation

Unforeseen Variations

- Not listed in the classification guideline
- Not classified as Type IB via Article 5 recommendation
- Justification for proposed classification in the application form

Note: If a condition for a Type IA is not met NOT unforeseen but 'default' Type IB

Article 5 *vs* reclassification

Art 5	***Art 3(2) & 3(3)(b)***
Classification within 45 days	'Reclassification' during validation (approx. 2 wks)
EMA, CMD, WPs, EC	EMA/MS only
Publication of each recommendation	No publication
Basis for other similar variations for CAPs/NAPs and update of the guideline	Basis for the update of the guideline

Practical Experience

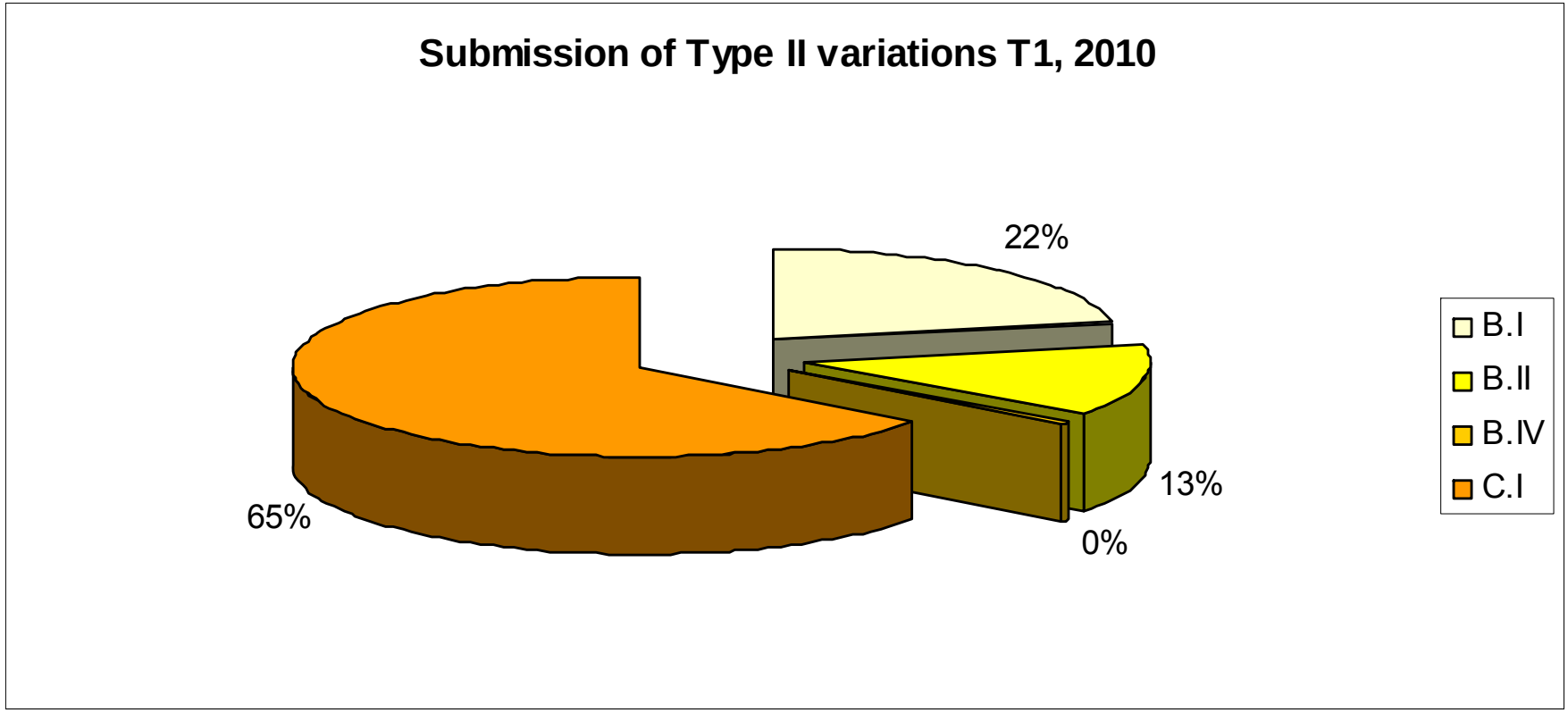
- No requests to the Agency for Article 5 recommendations!

Why?

- Request for advice from PTL/PTM before submission?
- Submission as Type II variation?
- Duration of procedure 45 days?
- Outcome binding?

- Agency involved in requests for Article 5 recommendations to CMDs

Type II variations



- Reduced by ~27% compared to the same period in 2009

Grouping

- Cases of acceptable grouping listed in Annex III *OR* agree with the Agency before submission
- Grouping should always be justified & **meaningful** to be reviewed simultaneously
- Quality, Non-clinical & Clinical cannot be grouped, unless justified
- Quality variations to active substance cannot be grouped with finished product, unless justified
- Grouping should **not delay the submission and implementation of safety information**

Practical Experience

➢ **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)
- ~ 50 requests on grouping

Practical Experience

- Consider carefully groupings proposed, i.e.:
  - ***Facilitate review of variations?***

- Avoid ‘super’groupings (e.g. extension + new indication + quality changes to active substance and finished product)
- If Type IA not directly related or consequential - Annual report
- No need to consult the Agency for groupings of Type IA notifications only!

Worksharing

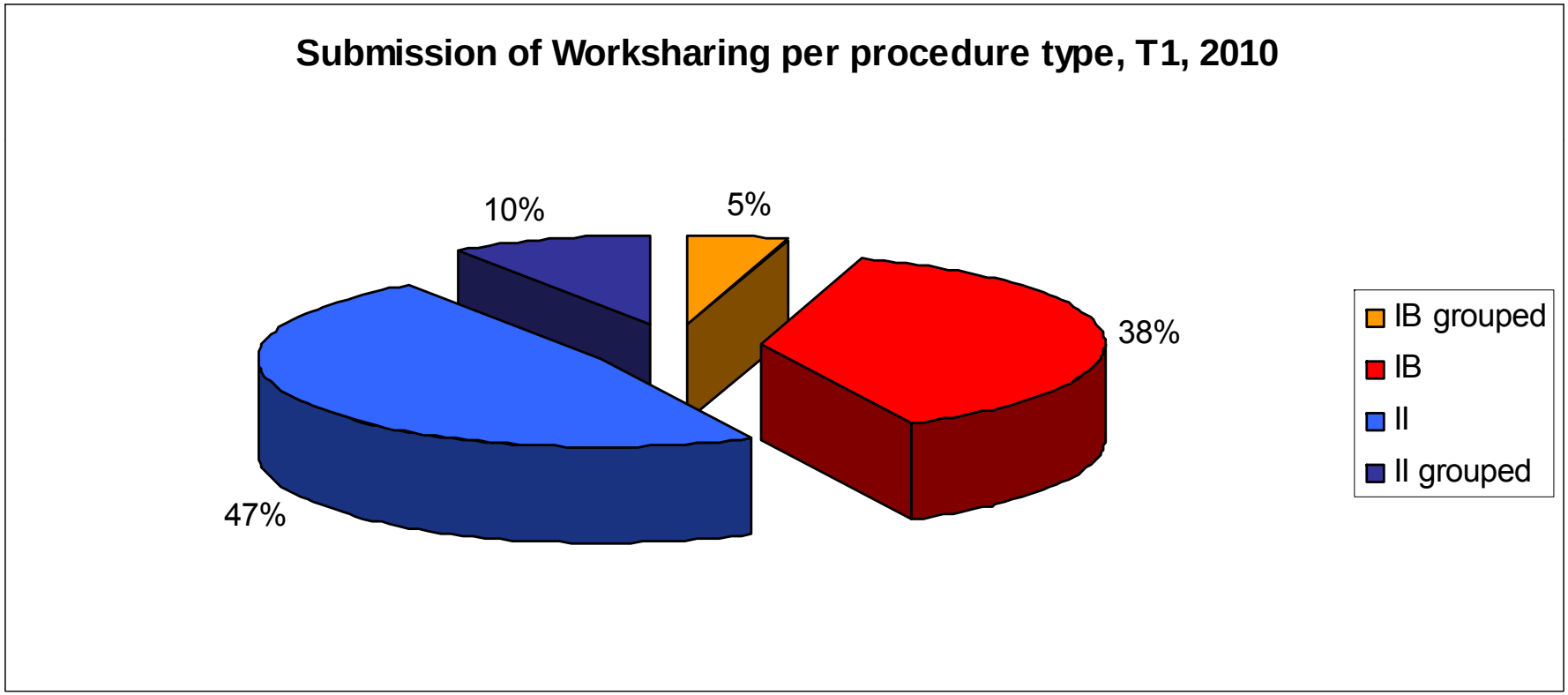
Same change(s) applying to different MAs

- **Same dataset**; no need for product specific assessment => Worksharing **OK**
- **Common dataset**, but with limited need to review impact on individual products => Worksharing **OK**
- **Separate datasets** for each individual product which require separate assessments => **NO** Worksharing

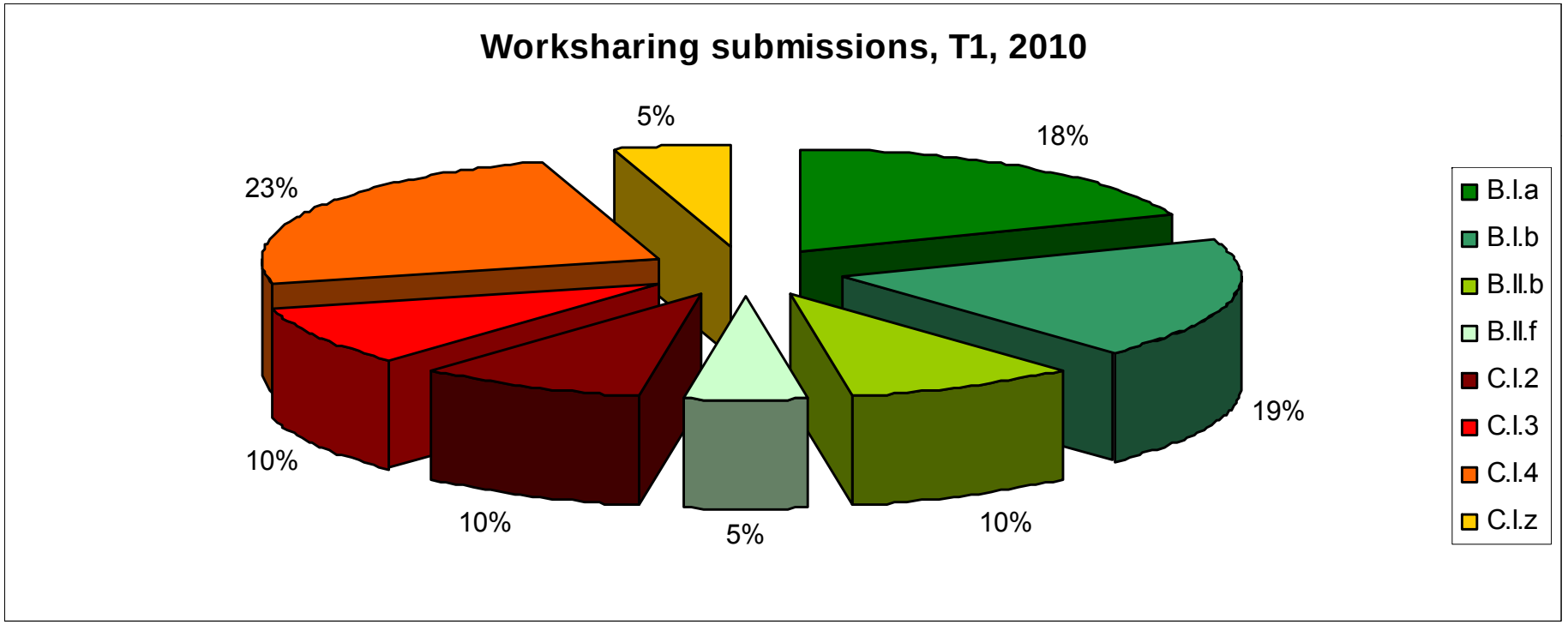
Worksharing

- Worksharing includes an average of 3 products
- Only 1/21 worksharing including MRP products
- Duplicates routinely accepted for worksharing
- ~ 38 requests on worksharing
- Examples of worksharings:
  - B.II.b.1, C.I.2, C.I.3

Worksharing



Worksharing



Points for discussion

- **Positive aspects:**

✓ Principles for classification of variations

✓ Downgrading of Variations

✓ Implementation of Variations

✓ Classification guideline for individual changes

✓ Type IA ‘Do and Tell’ & Annual report

✓ Type IB by default

✓ Worksharing

Points for discussion

- **What needs to be improved?**

➢ Need to simplify submission & handling of multiple changes/groupings?

➢ Classification guideline & application form not optimal for multiple changes/grouping?

➢ Increase submission of Type IA notifications as part of Annual Report!

➢ Others?

Conclusion

- The Agency is committed to contribute to achieve aim of new Variations Regulation
- Continue to participate in CMD Variation Sub-group
- Ensure a harmonised approach with MSs on classification of variations, Article 5 recommendations, grouping and worksharing
- Contribute to the revision of the classification & procedural guidelines

Thank you very much!

Any questions?

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