Science For A Better Life

The revised Variation Regulation

Industry perspective on the first year of experience

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Agenda/ Content

- Objectives of the revision, Scope
- Classification / Grouping / Workshare
- Article 5 to classify unforeseen variations / DDPS
- Implementation of labelling changes after MRP
- Registration fees
- Objective reached ? What else is needed ?

Objectives of the revision of the Variation Regulation

Commission Regulations (EC) 1084 & 1085/2003

- on CP, MRP products – not nationally approved products
- considerable burden for industry and authorities (large number of variations)

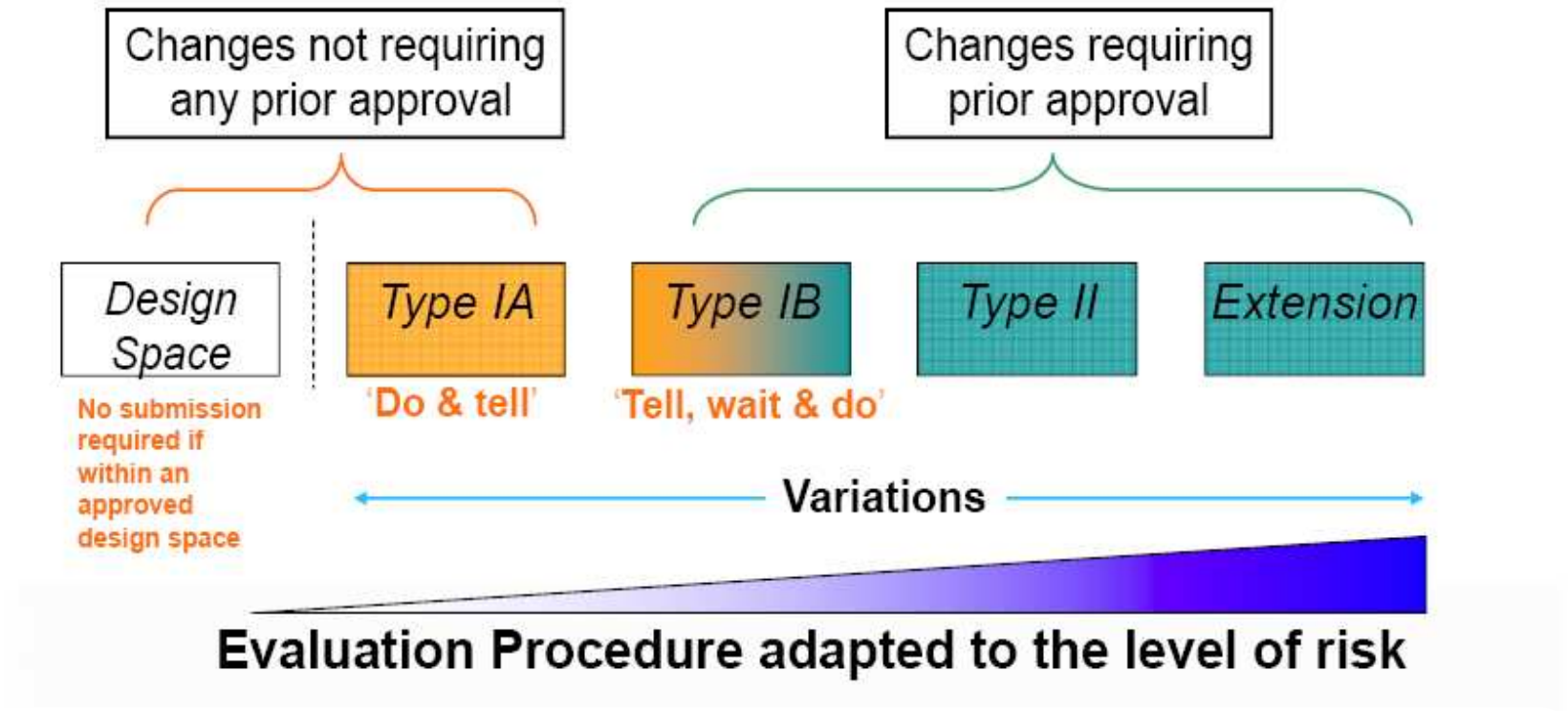
Commission: Review project launched in 2006

“Better Regulation“ with following objectives:

- Clearer, simpler, *more flexible*
- Reduce administrative burden
- Adapt to ICH concepts (Q8, Q9, Q10)
- Further harmonise handling of variations in EU

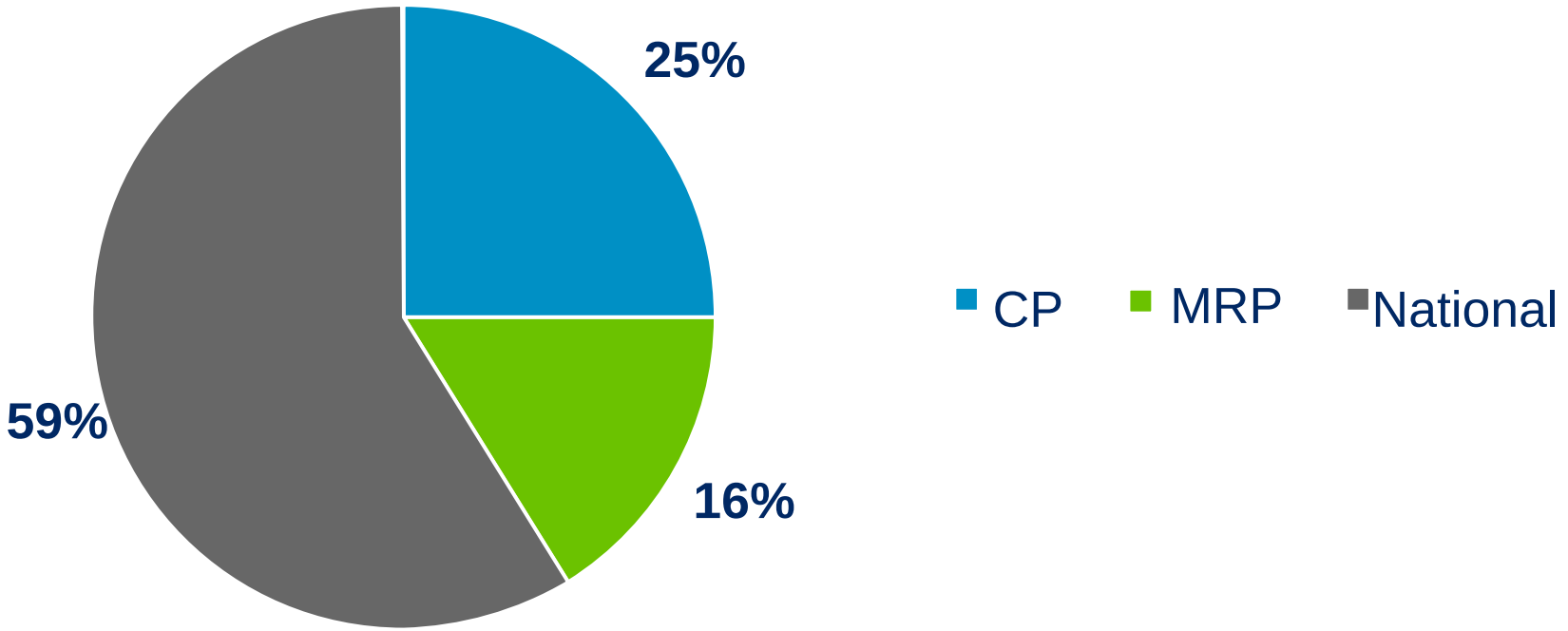
« *without compromising human and animal health* »

A risk based concept



[after K.Pugh, MHRA, March 2011, DIA Geneve]

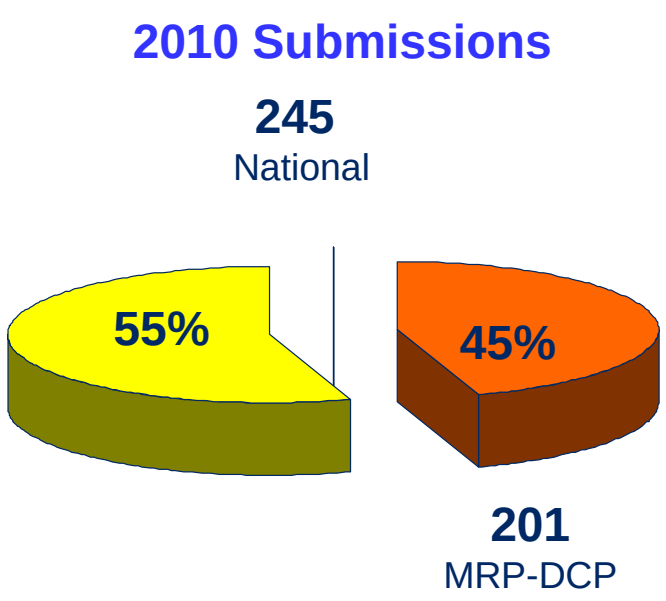
Scope of Regulation – BHC Pharma Portfolio

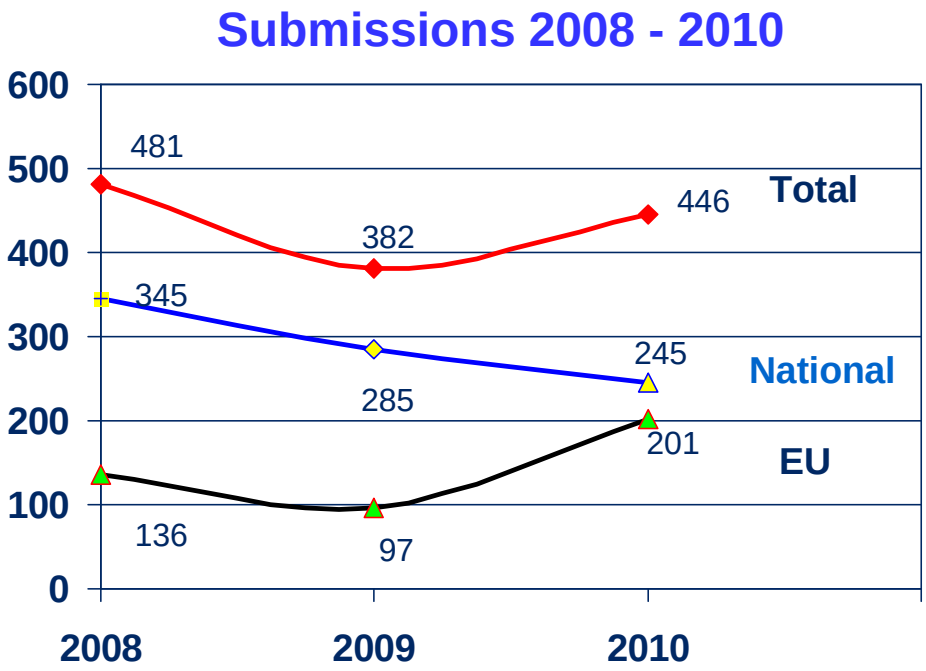


Percentage of overall number of drug product licenses, Status: August 2009

Workload on national and MRP/DCP products – a BHC affiliate´s example

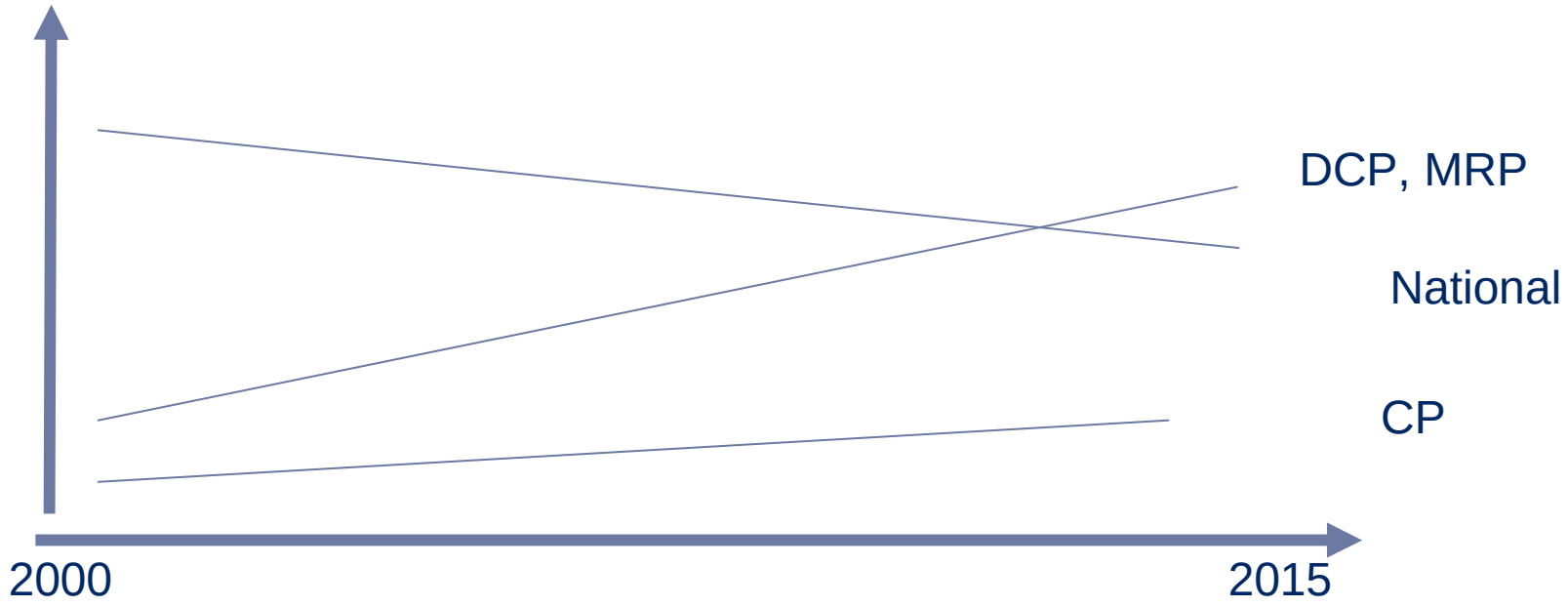
- Number of Regulatory submission activities (I.e. CMC and labeling changes and renewals, including OTC portfolio)





Variation workload only slowly shifts to EU procedures

- More EU procedures after Nov 2005 (MRPs, CPs) while national maintenance procedures remain (graph is descriptive only)



National / MRP portfolio mix difficult to handle with the new variation regulation

Inclusion of national procedures will be critical for efficiency gains

Overview of national use of EU Var. Reg. 1234/2008/EC		
Yes: 12/29 MSs	**Yes, but different timelines:** 9/29 MSs	**No** 8/29 MSs
BE, CY, EE, EL, HU, IT, LU, NL, SK, SL, UK, LV	DK, ES, FI, IE, IS, LT, MT, NO, SE	AT, BG, CZ, DE, FR, PL, PT, RO

- Implementation for national procedures currently based on voluntary action by MS
- Directive 2009/53/EC empowers EU Commission to make the variation regulation mandatory for MS by amending it`s scope – not yet executed

Classification - clear improvements on efficiency

- Type IA - Do and tell
- Type IB by default
- Downgrade of Type II
- 12 months reports (Annual reports)

Grouping

- 23 groupings requested by BHC Pharma so far
  - All proposals accepted
  - Validation times not always adhered to
  - List of proposed groupings: positive trend in widening of the spectrum (i.e. outcome of workshares, manufacturing site changes)

Proposal to Competent Authorities: Opportunities could be further expanded

- Increase options on consequential changes
- Be flexible on validation of Type IA variations - flexibility comes without risk as these are minor changes
- Allow submission as one single group, even if the RMSs are different in particular for Type IA (IN)
  - Example: change of name or address of a MAH in one country affecting many products
- Include **all** national procedures as soon as possible

Worksharing

- 11 procedures initiated by BHC Pharma so far
  - All accepted
  - Validation times not always adhered to

Proposal to Competent Authorities: facilitate initiation of Worksharing (WS) and fully exploit opportunities

- Reduce lead time of 3 m or even 6 m advance notice
- Use of the Type IB timetable instead of the Type II timetable especially in case for worksharing of an original + duplicate (currently Type II 60 day by default)
- Include **all** national procedures as soon as possible

Article 5 to classify unforeseen variations

- Too lengthy process – 30 day procedure should be enough
- Too many bodies involved in decision making (EMA, CMDh)
  - appreciated that CMDh reaches agreement by majority votes

- Current set up will lead to more Type II submissions than really required

  In case of doubt companies...
  - will often not have the time to wait until Art 5 clarification
  - can also not afford the delay from a potential resubmission (if a Type IB is upgraded and then has to be resubmitted as Type II)

Detailed Description of the Pharmacovigilance System (DDPS)

- In the past all changes were by default Type II, now most changes are defined as Type IA or Type IA(IN) - except change of QPPV Type IB ☺
- New CMDh template on prior assessment of the DDPS is supportive ☺
- „Type I A_{IN} to be submitted immediately after implementation“
  - Interpretation of „immediately“ varies
  - Some documents will only become available after implementation
  - Logistic challenge to submit simultaneously individual variations for the entire portfolio – best efforts will always be made
- Implementation of the Pharmacovigilance legislation: no need for a DDPS summary in individual dossiers if the Master file concept will be set fully effective (all data will be available for PV inspections)

BHC Pharma survey - Implementation of MRP labelling changes after EU approval

BHC Pharma internal survey Q1 2011 on procedures initiated in 2010

Type IA - no issues

Type IB - should require no national phase, however 20 % of affiliates are reluctant to implement changes

- used to get later comments from some member states on national level after RMS approval
- some official national documents are received only after 150 days (still within 6 m)

Type II - majority of MS do not comply with the 60 day national phase, up to 120 days till approval arrives and many still pending

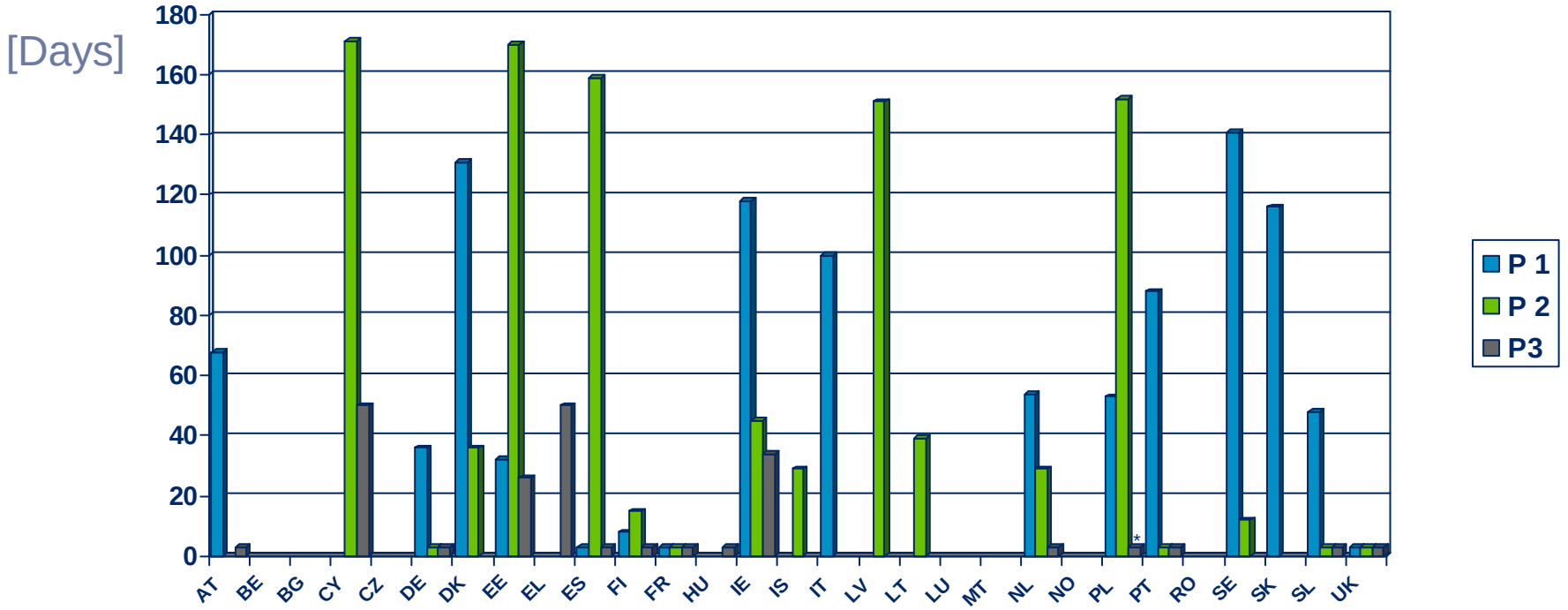
- 60 % of country affiliates would not proceed for implementation after 30 days but would continue to seek consent with authority first

The company has to balance the benefit of timely patient information on relevant safety and efficacy changes versus the risk to implement too early and rework / recall material

Type IB Labeling variation: Time to national green light after RMS approval

Example from 3 MRPs initiated at BHC Pharma in 2010

Regulation: MA holder may implement after acceptance (or deemed acceptance), CA to update MA within 6 m

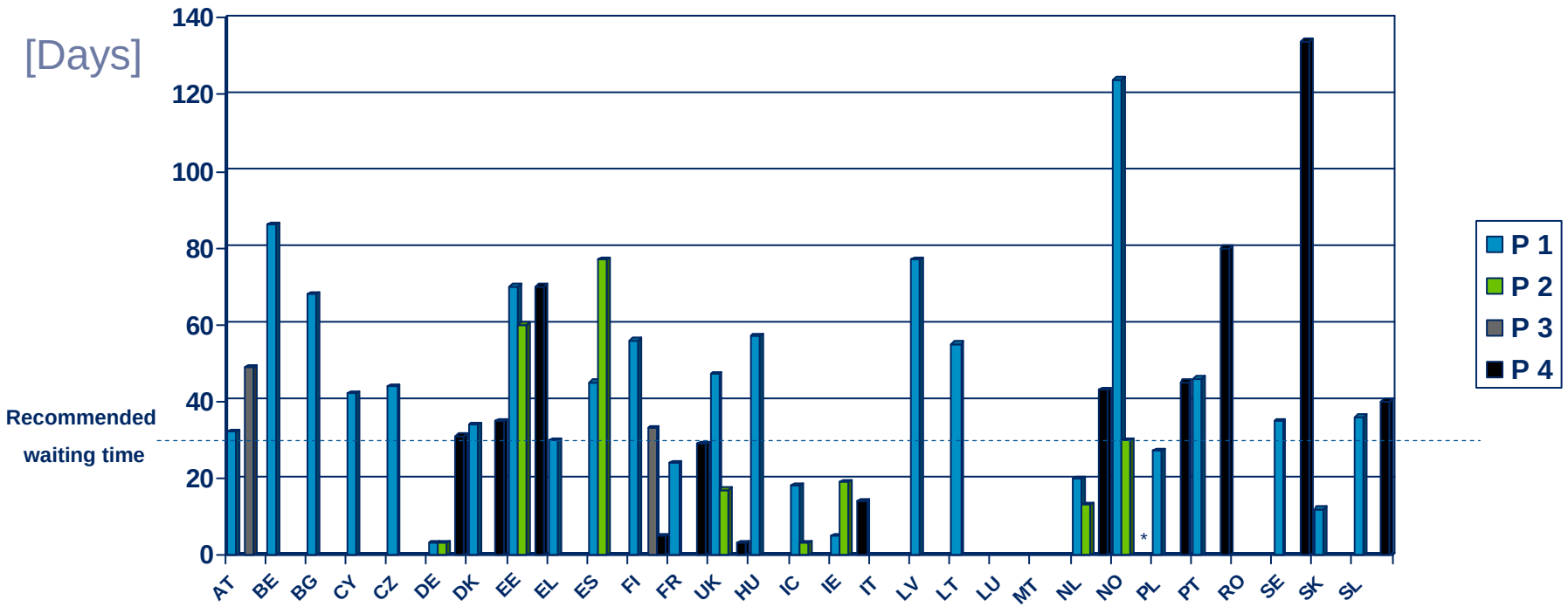


Missing values = no involvement or agreement on acceptance not yet achieved

Type II Labeling variation: Time to issue of national approval after RMS approval

Example from 4 MRPs initiated at BHC Pharma in 2010

Regulation: MA holder may implement after 30 d, CA to update MA within 60 d

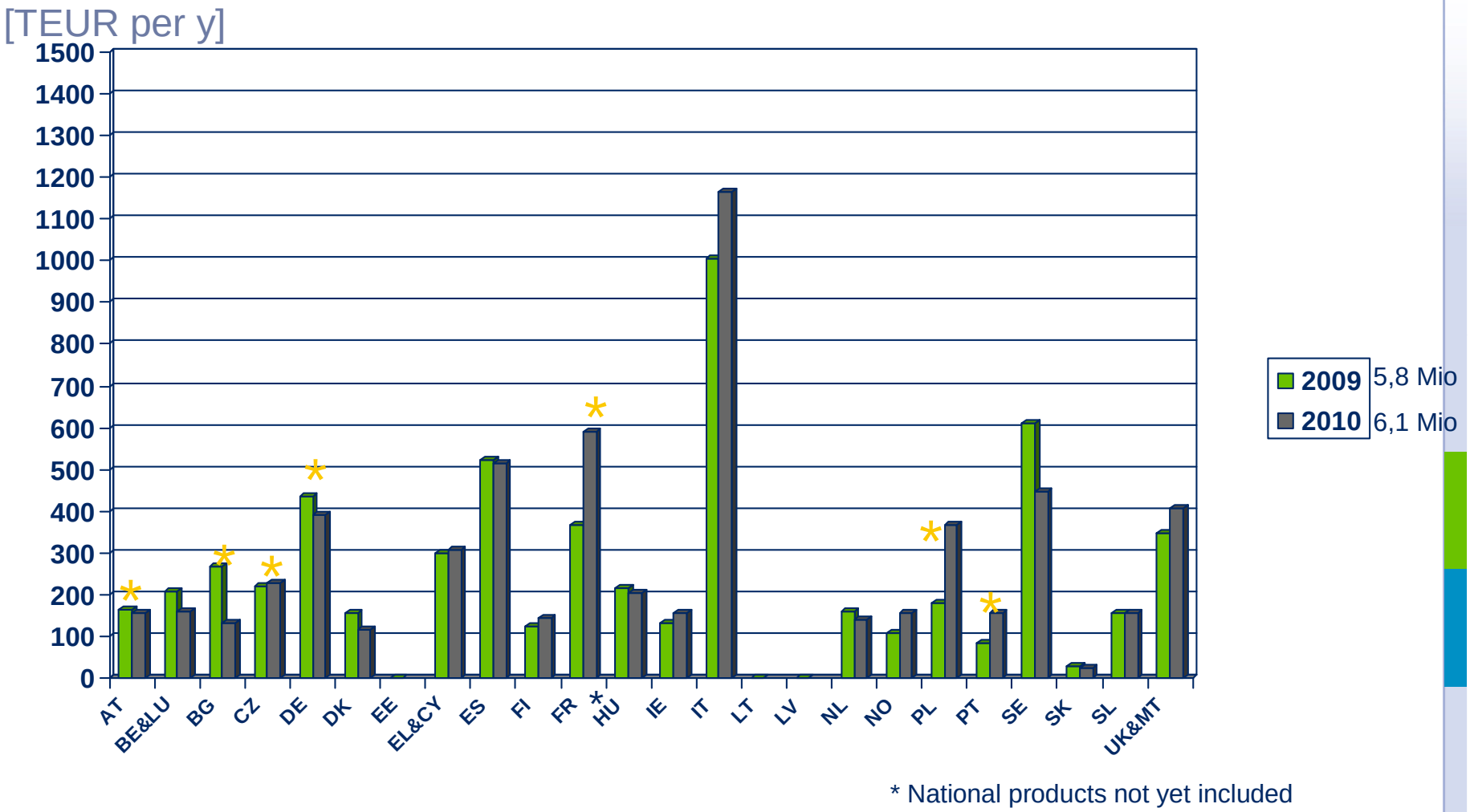


Missing values = no involvement or approval not yet achieved

Fees

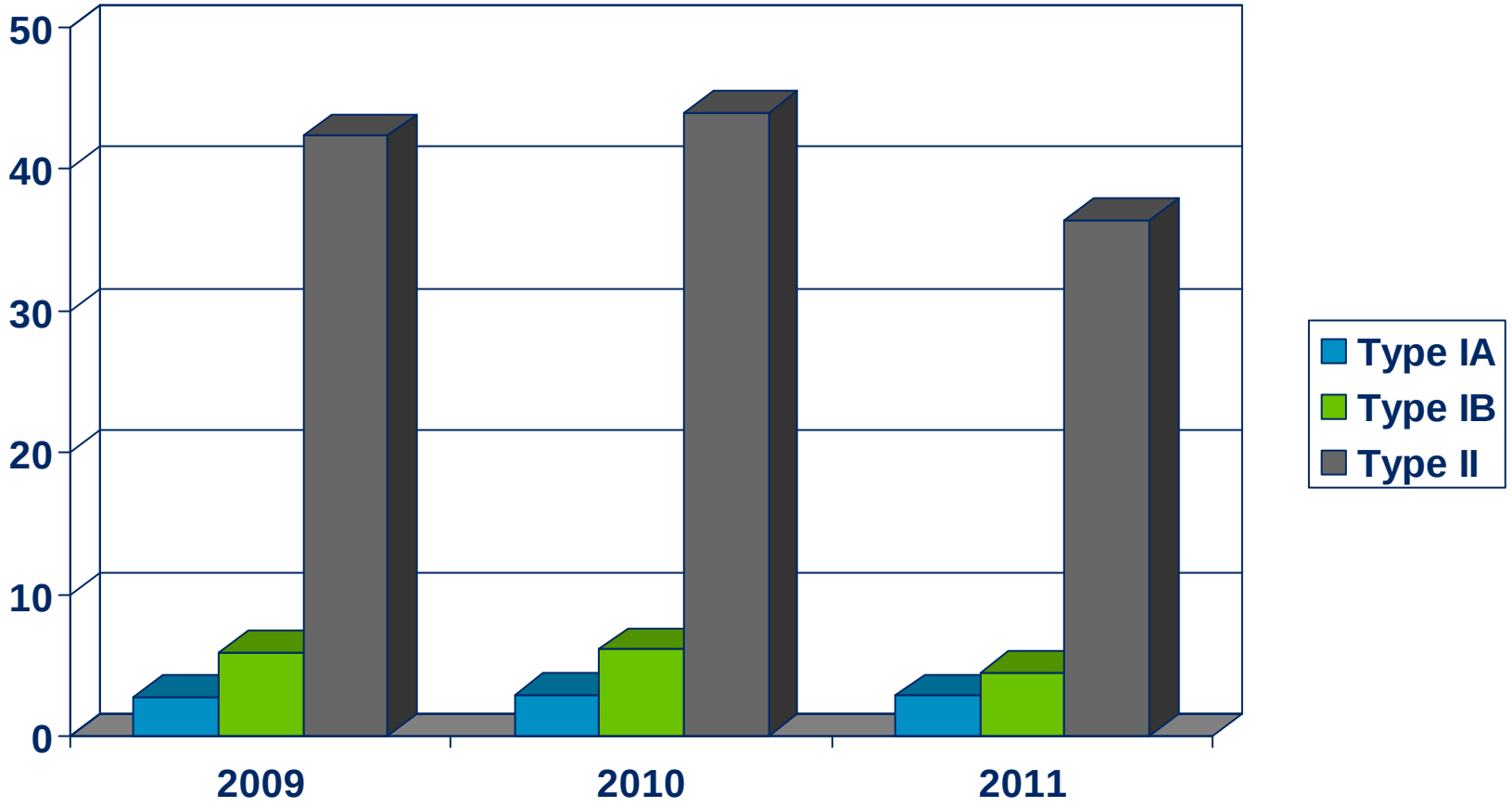
- Costs increased rather than decreased due to new definitions, i.e.
  - Authorities no longer accept several changes (consequential changes)
    - i.e. several changes in the interaction section of the SmPC can not longer be combined as one variation even if resutling from same CCDS
    - A series of CMC changes can not longer be combined to one Type II change
    - DDPS change to new QPPV and his contact details handled as two variations
- Efficiency gains from new variation regulation are not yet leveraged in fee schemes
  - No reduced fees for same change across Marketing Authorizations
  - No synergy on costs from grouping or annual reports
- Positive examples:
  - Reduced costs for workshare of duplicates with same MAH (EMA)
  - Slightly reduced costs for WS and grouping (EMA)

BHC Pharma - EU countries Registration Fees (TEUR) rather increased from 2009 to 2010



BHC Pharma - EMA fees – small reductions per variation from grouping / WS expected only in 2011

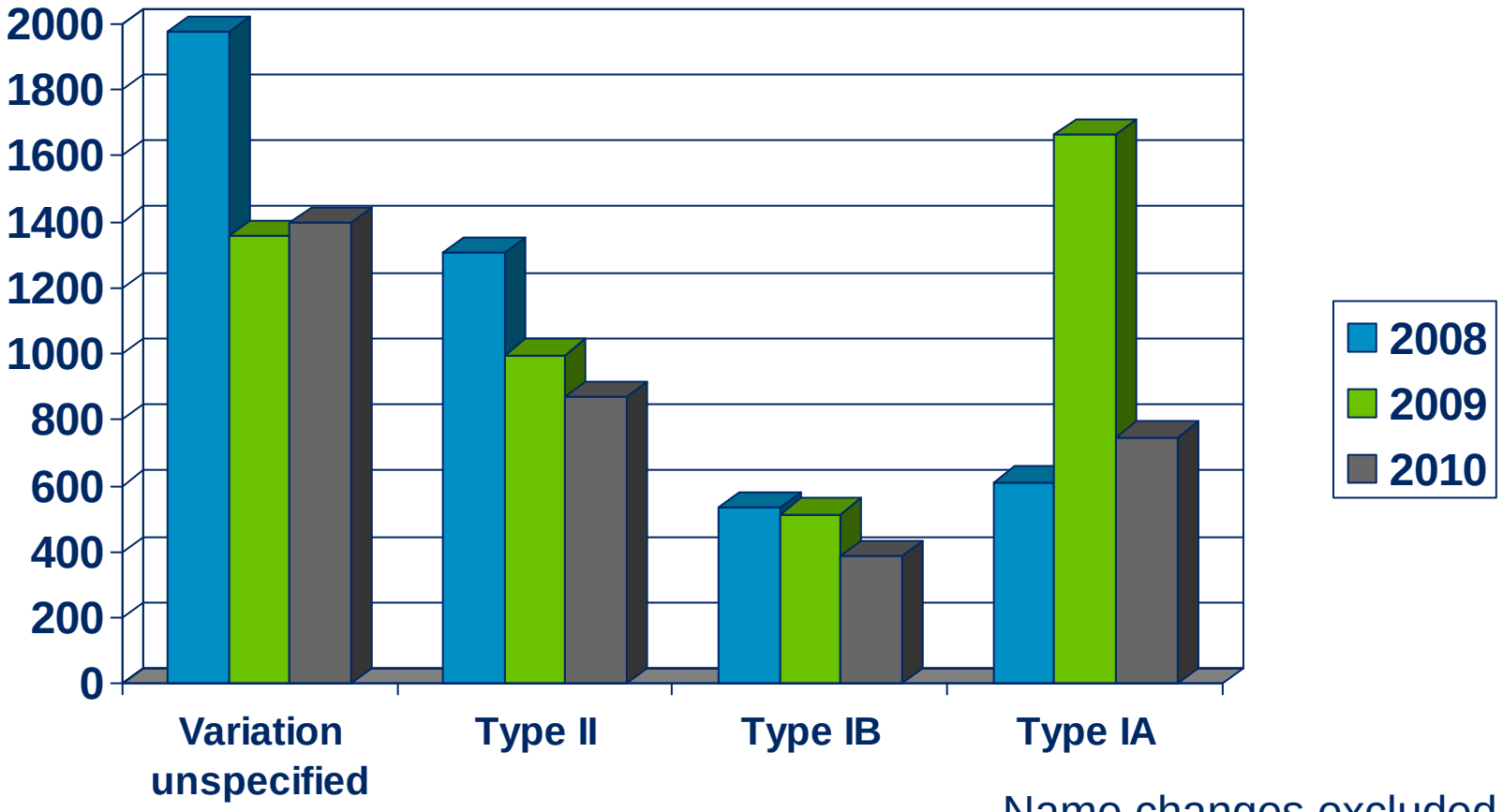
[TEUR per EMA variation, mean of all variations submitted per year]



2011: Plan data

BHC Pharma EU - # of variations (MRP, National) - trend towards less variations

[numbers per year]



Name changes excluded

Variation regulation - Conclusion

"Better Regulation" with following objectives:

- Clearer, simpler, *more flexible* 😐 Type I B by default and Type IA do and tell ☺
- Reduce administrative burden 😐 Fees ☹ …with nationals 2013 ☺ ?
- Adapt to ICH concepts (Q8, Q9, Q10) 😐
  - Examples for design space for biological finished products ?
  - Acceptance of change management protocols ?
- Further harmonise handling of variations in EU ☹…with nationals included 2013 ☺ ?

« *without compromising human and animal health* » ✓☺

Industry and agencies have not yet learned to use all flexibility and opportunities of the revised variation regulations – too early to judge and progress is slow

Behavioural changes needed to effectively use the risk based approach of the regulation

- **For optimal use, Regulatory Authorities need to**
  - **Leverage procedural knowledge and risk based approach to all assessors**
  - **Judge risk and use the Type IB as default**
  - **Be flexible on validation issues for Type IA**
  - **Fully accept RMS assessments**
    - **no further requests after closure of EU process in particular for for Type IB (also not on translations)**
  - **Provide earlier feedback on Type II changes**
    - **resource issues must be solved first in many Regulatory authorities**
    - **i.e. review translations asap**
    - **no further requests after 30 days**

Behavioural changes needed to effectively use the risk based approach of the regulation

- **For optimal use, companies need to**
  - **Leverage procedural knowledge in all functions**
  - **Judge risk and use the Type IB as default**
    - Only if significant impact on safety and/or efficacy use Type II
    - Decide and justify, ask MS authorities but avoid to initiate Article 5 unnecessarily
  - **Plan changes as proactively as possible based on risk assessment (for grouping, workshare, annual report)**
  - **Establish more refined tracking systems that link change management, logistics and Regulatory procedures even more than in the past (specifically for EU)**

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Thank you!