Revision of the EU Variations Regulations – Outcome of the Consultation Procedure and Further Steps

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Structure

- Where it all started....
- The Co-Decision Part
- The Comitology Part
- Summary and outlook

Where it all Started....

- Last revision of Variations Regulations in 2003 with the aim to simplify the system
- Global review of Community pharmaceutical legislation ("Pharma Review") in 2003 – 2004
- Need to assess how far aim of 2003 revision has been achieved, based on
  - feedback from stakeholders
  - internal experience within the Commission
  - regulatory developments at international level, e.g. ICH

Where it all Started....

- Part of the Commission Simplification Rolling Programme for 2006-2009 and of Commission Legislative and Work Programme 2008
- EC-Objectives:

  - clearer, simpler, more flexible
  - reduce administrative burden
  - create legal basis to embrace ICH concepts
  - further harmonisation between EU Member States

without compromising human and animal health

Aim of the Review

- Single regulatory text, covering changes to all marketing authorisations
  - human/veterinary
  - centralised
  - decentralised/mutual recognition
  - national

Key Items of the Review

1. Application to national authorisations
2. ICH Q8 – Q9 - Q10
3. ‘Do and Tell’ Procedure
4. Single evaluation of common changes
5. Type IB by default
6. Other aspects, e.g. variations conditions

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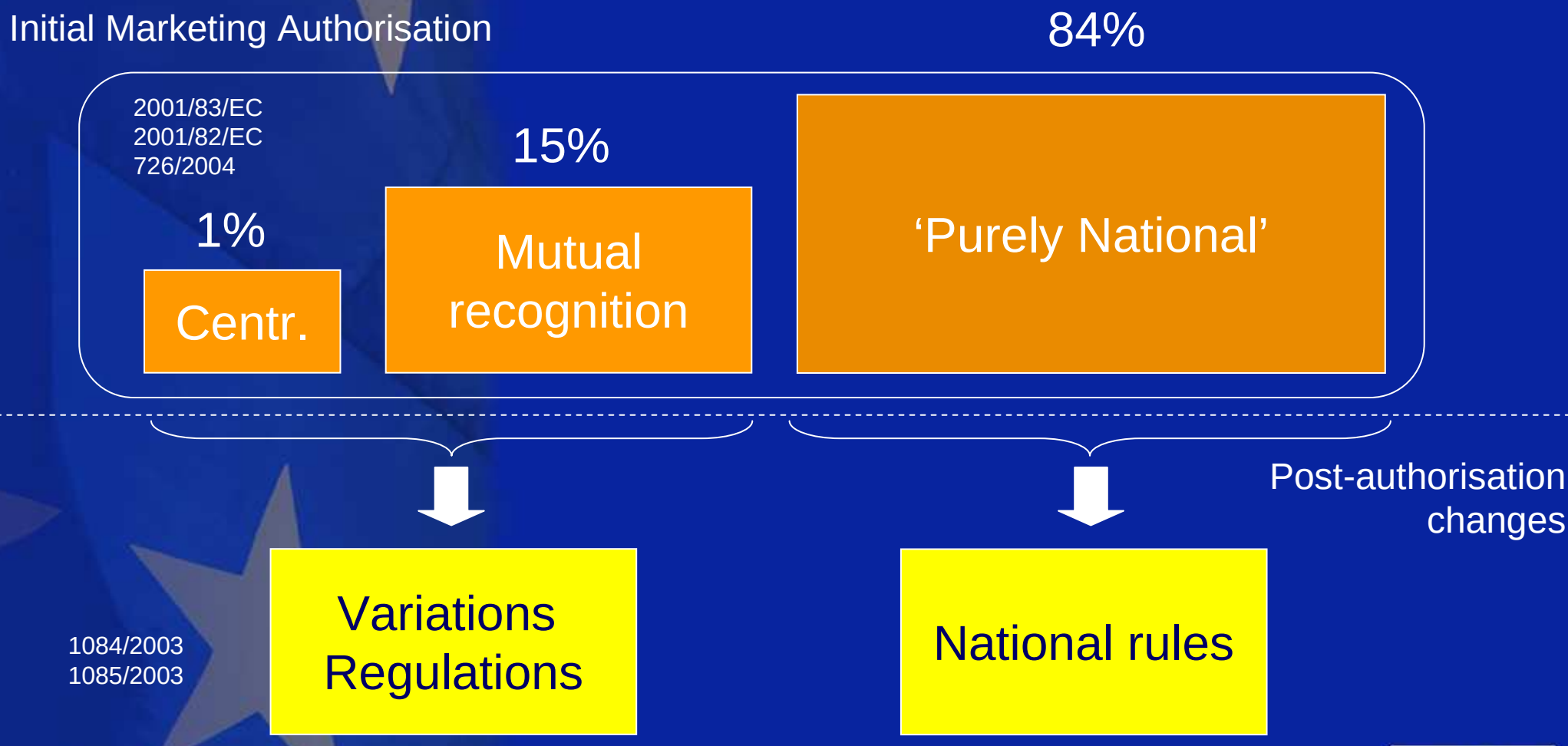
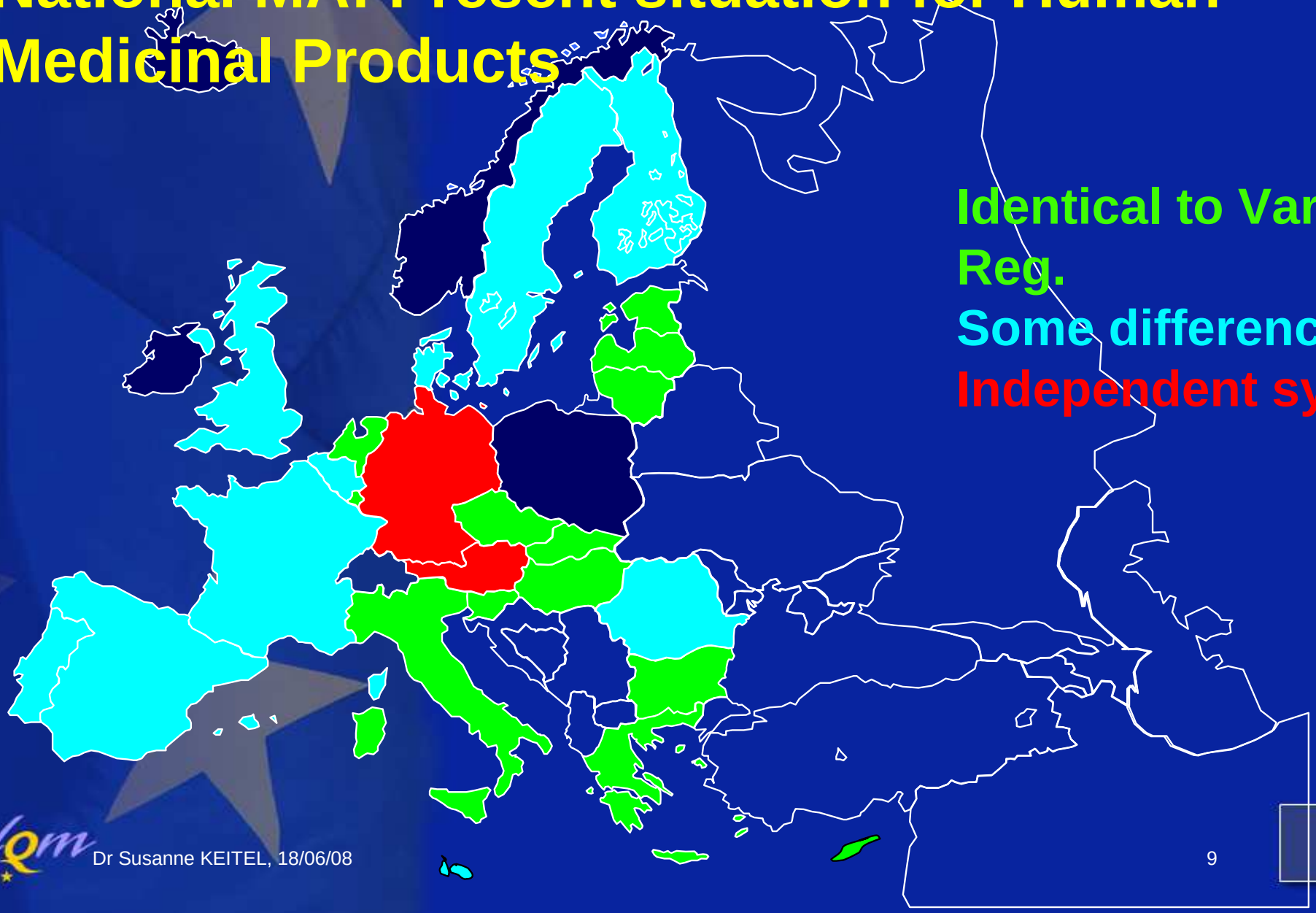
Key Item 1: Harmonisation



Source: EU-Commission

National MA: Present situation for Human Medicinal Products

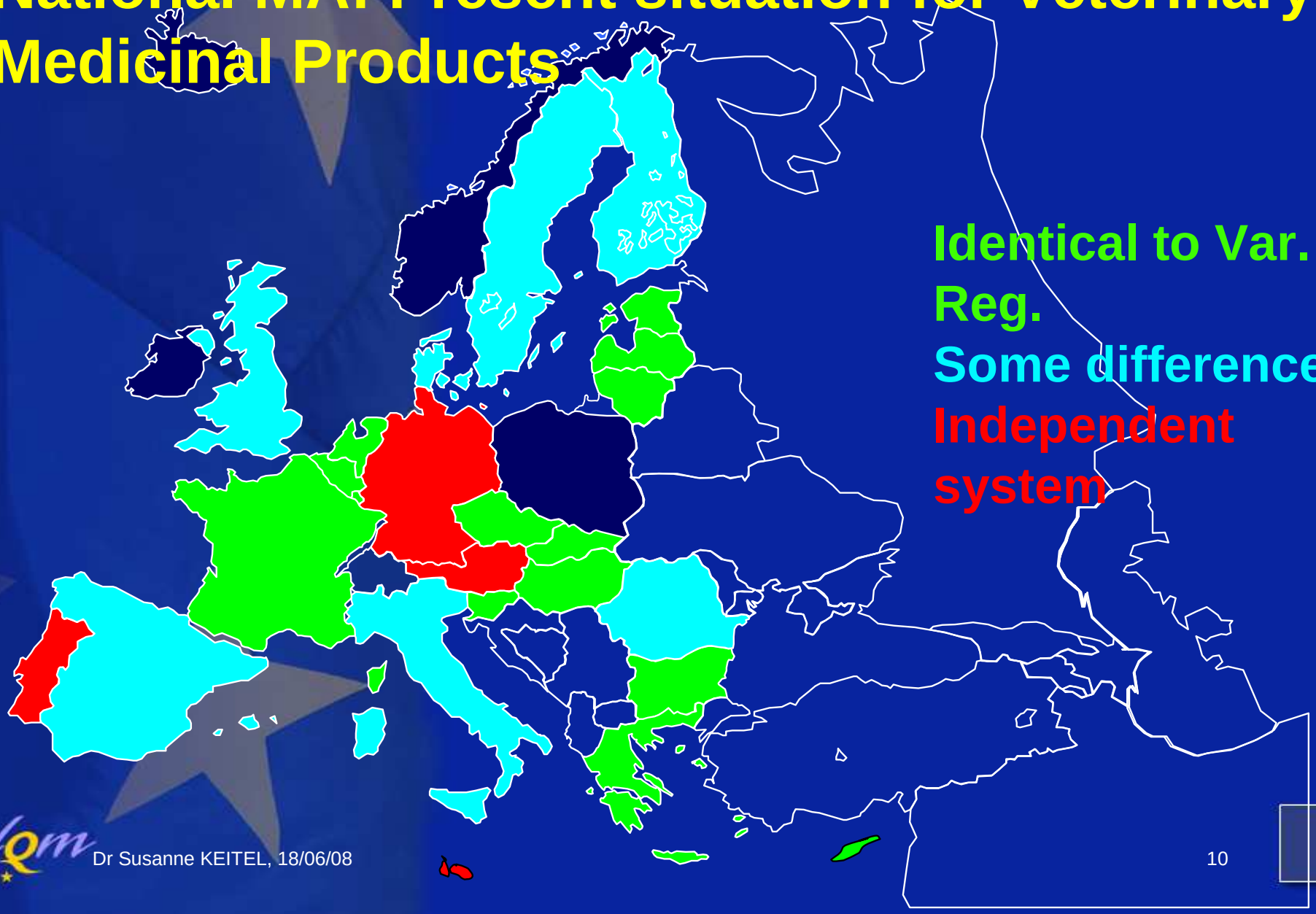


Identical to Var. Reg.

Some differences

Independent system

National MA: Present situation for Veterinary Medicinal Products



Identical to Var. Reg.

Some differences

Independent system

Necessary Legal Strands …

1

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

→ **Co-decision procedure**

2

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

→ **Comitology**
Regulatory procedure
with scrutiny

Source: EU-Commission

Commission Proposal of 4th March - (1)

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 4.3.2008
COM(2008) 123 final

2008/0045 (COD)

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending Directive 2001/82/EC and Directive 2001/83/EC as regards variations to the terms of marketing authorisations for medicinal products

(presented by the Commission)

{SEC(2008)273}
{SEC(2008)274}

Commission Proposal of 4th March - (2)

Article 2

Amendments to Directive 2001/83/EC

Directive 2001/83/EC is amended as follows:

(1) The following Article 23b is inserted:

"Article 23b

The Commission shall adopt appropriate arrangements for the examination of variations to the terms of marketing authorisations granted in accordance with this Directive.

These arrangements shall be adopted by the Commission in the form of an implementing regulation. This measure, designed to amend non-essential elements of this Directive, by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a)."

(2) In Article 35(1), the second and third subparagraphs are deleted.

Commission Proposal of 4th March - (3)

Article 3

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by [12 months after entry into force] at the latest. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

   When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 4

This Directive shall enter into force on the [twentieth] day following that of its publication in the Official Journal of the European Union.

Co-Decision Part - Procedure

1. Public Consultation (Start: July 10, 2007)
2. Outcome of the Public Consultation (October 3, 2007): 19 written responses
3. Adoption of the Commission proposal on variations (March 4, 2008)
4. Submission of the Commission proposal to Council and Parliament
5. Council discussion during the Slovenian and French Presidency

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Comitology Part – The Process (1)

1. Public Consultation (Start: October 25, 2007)
2. Outcome of the Public Consultation (January 14, 2008): 48 written responses + discussion with Pharm Committee, HMA, NtA, CMD and Industry
3. First discussion of an incomplete draft of the EC (April 3, 2008) in the Standing Committees

Comitology Part – The Process (2)

4. Discussion in the Standing Committees June 2, 2008
5. Adoption of a slightly modified proposal by Standing Committees on June 10, 2008
6. Scrutiny by European Parliament and Council until September 13, 2008
7. Adoption by Commission and coming into force

Comitology Proposal
- The Outcome -

Scope of the New Variations Regulation

- "ex-concertation" products, MRP, DCP and CP
- Authorisations granted following a referral (Articles 32 to 34 Dir. 2001/83/EC)

Outside scope:

- change of the MAH
- changes to **registered** homeopathic and traditional herbal medicinal product ("for reasons of proportionality…", recital 2)

Key Item 2: ICH Q8 – Q9 – Q 10

Design space

- Variations related to the introduction of a new design space or the extension of an approved one classified as type II (annex II)
- Variations within an approved design space not considered a change (but where does it say so?)

Key Item 2: ICH Q8 – Q9 – Q 10

Design space

- Variations within an approved design space not considered a change
  but where does it say so?
  Annex II f) states:
  "Variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines"

Key Item 3: “Do and Tell“ (Type IA)

- Can be implemented prior to notifying authorities
- Notification either
  - Within twelve months following the implementation of the variation (“annual report”)
  - Immediately after implementation for minor variations requiring immediate notification for the continuous supervision of the medicinal product, e.g. change of address...

Key Item 4: Single Evaluation of Common Changes (Grouping and Worksharing)

- Grouping possible for
  - same type IA variations to one or several MA‘s
  - several variations to one MA

  for the same MAH
- Classification according to the highest level of the individual submission type

Worksharing - (1)

- for Type IB, Type II and grouped variations
- Evaluation by “reference authority”
  - EMEA (at least one MA involved centralised)
  - CA of MS, selected by CMD “taking into account a recommendation of the holder”

Worksharing - (2)

- Evaluation by “reference authority” (cont’d)

  If CA from Member State selected which has not granted a MA for all products concerned, CMD may request another CA to assist in the evaluation

Worksharing - (3)

- Procedure
  - submission of application to all CA concerned
  - validation by “reference authority” only
  - (normally) timeframe of a Type II-variation
    - possibility of a clock stop
    - scientific opinion within 60 days (standard procedure)
    - reduction (safety, 30 days) or extension (indications, 90 days)
  - Concerned Member States shall approve the opinion of the “reference authority” within 30 days or raise a potential serious risk to public health (resulting in a CMD referral)

Key Item 5: “Type IB by Default“ - (1)

- List for type IA and type II variations (annex II)
- Exhaustive list of line extensions (annex I)
- Guidelines on the details of the various categories to be elaborated in consultation with Member States and EMEA

“Type IB by Default“ - (2)

- Undefined changes by definition type IB

  BUT considered type II if variation not classified after application of the rules defined in the Regulation in case

  - CA/EMEA considers change to have a significant impact on quality, safety or efficacy during validation
  - requested by applicant

“Type IB by Default“ - (3)

alternatively:

- MAH or CA may ask CMDs/EMEA for a scientific recommendation on the classification of unlisted changes prior to submission or examination of a variation
- scientific recommendation (consistent with the guidelines referred to in art. 4(1)) within 45 days

“Type IB by Default“ - (4)

- EMEA and CMDs to cooperate to ensure coherence of recommendations
- scientific recommendations to be published following deletion of commercially confidential information

Other Suggestions of the "Issue Paper" - (1)

- Variations conditions: reclassification type IB to type IA partly achieved, further work needed
- Variations conditions for biologicals: partly achieved, further work needed
- CMDs: gain more important role, e.g. in the elaboration of recommendations for the classification, co-ordination of worksharing, referrals

Other Suggestions of the "Issue Paper" - (2)

- Monographs and Certificates of Suitability: partly achieved with annex II, further action in guidelines
- Clarification of deadlines on amendments for authorities: 30/60/180 days
- Clarification of deadlines for MAH: implementation dates

Final Provisions

- Introduction of notion of “Continuous monitoring“
- Review foreseen within 2 years after coming into force, focussing on classification of variations and possible need for amendments to annexes
- Applicability: 1 year after coming into force (except recommendations on unforeseen variations)

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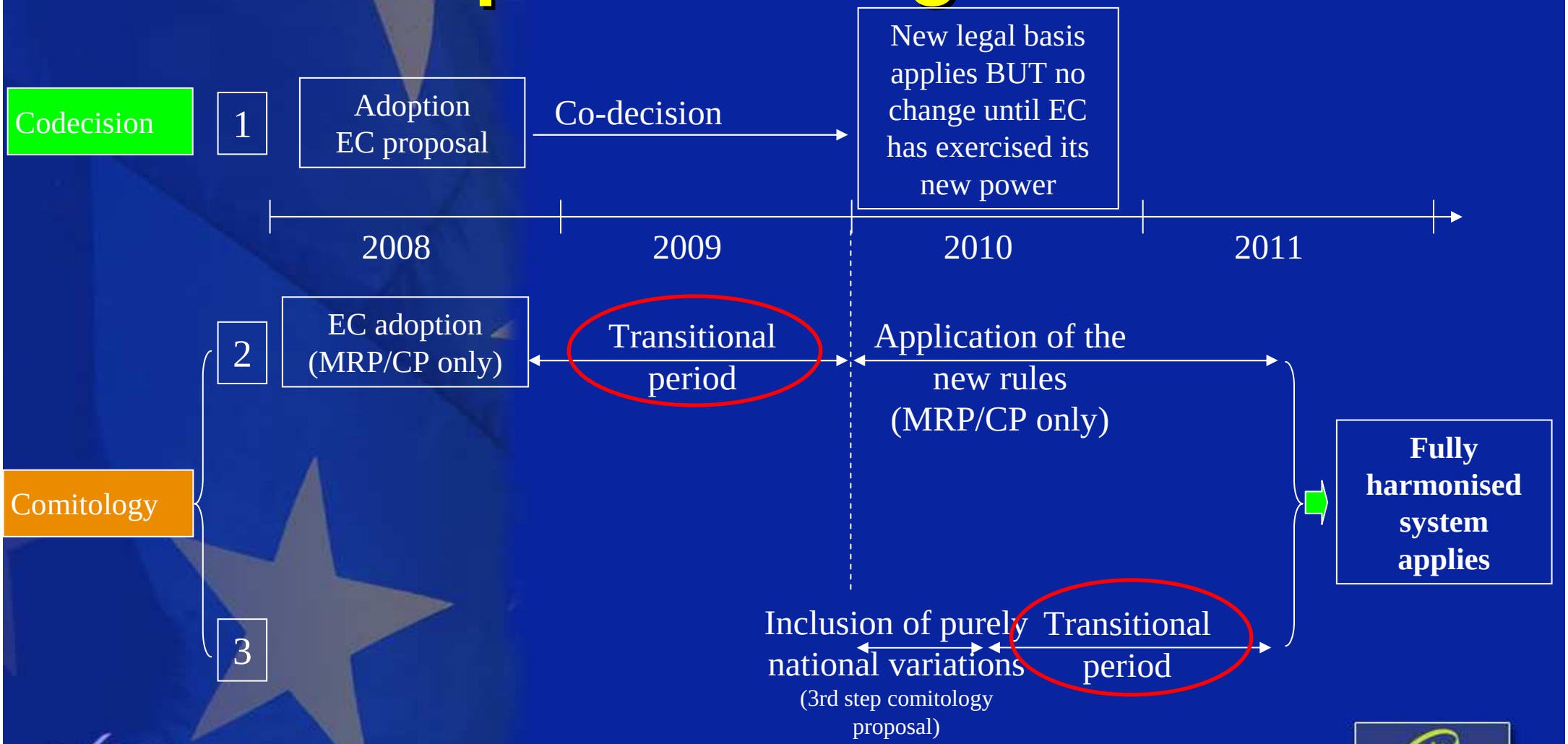
Next Steps & Timing



Source: EU-Commission

Next Steps …

- Co-decision:
  - ongoing discussion in the Council
- Comitology:
  - scrutiny procedure by EP and Council until Sept. 2008
  - coming into force IV/2008
  - applicable to MAH 12 months later
- Further work on other items:
  - Guidelines (classification of variations)
  - Fees (Council Regulation for the centralised procedure)
  - Consequences on MS fees???

Need more Information?

http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

Thanks a lot to

Dr. Peter Bachmann (BfArM)

Nicolas Rossignol (EU-Commission)

And YOU for your attention!