The new variation system – Impact on NCAs

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Introduction

- Commission Regulations (EC) 1084 & 1085/2003
- Considerable burden for industry and authorities
- Review project launched in 2006 by EC

EC-Objectives:

- clearer, simpler, more flexible
- reduce administrative burden
- adapt to ICH concepts
- further harmonisation

without compromising human and animal health

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Aim of the Review

- single regulatory text, covering changes to all marketing authorisations
  - human / veterinary
  - centralised
  - decentralised /

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necessary legal strands …

1. Review of the legal basis of the Variations Reg. (2001/83/EC, 2001/82/EC, 726/2004) = common set of rules for variations, regardless of autorisation route of the product → **Co-decision procedure**
2. Review of the content of the Variations Reg. (1084&1085/2003) → **Comitology Regulatory procedure with scrutiny**

Source: EU-Commission

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Key Items of the Review

Radical and concrete approach to simplification

1. Harmonisation to national authorisations
2. Design space (ICH Q8 – Q10)
3. 'Do and Tell' and 'Annual Report'
4. Worksharing (incl. Grouping)
5. Type IB by default

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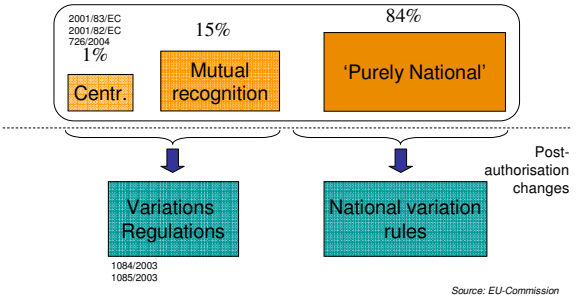
The New Variation Regulation (Codecision proposal)

Key Item 1: Harmonisation

Initial Marketing Authorisation



Source: EU-Commission

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Current situation with national variations

- Independent System
  - eg. AT (§ 24 AMG), DE (§ 29 AMG)
- Mixed System
  - categorisation of changes according to CR 1084/2003 - but different time lines
- Full Implementation of CR 1084/2003

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Current variation system in DE

The current variation system in Germany is a smooth, unbureaucratic and effective system

- ⇨ based on the legal self-responsibility of the MAH
- ⇨ based on a defined list of major variations whole rest are simple notifications
- ⇨ implicit approval of approval procedures after 3 months

- Germany has high interest in achieving a European system as simple as the national one

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Co-decision part – current status

1. Public Consultation (Start: 10 July 2007)
2. Outcome of the Public Consultation (03 October 2007): 19 written responses
3. Adoption of the Commission proposal on variations (04 March 2008)
4. Adoption by the European Parliament (22 October 2008)
5. Council discussion during the Slovenien and French Presidency

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Where to find published informations?

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


Review of the Variations Regulations

Better regulation of pharmaceuticals: towards a simpler, clearer and more flexible framework on variations

22 October 2008: Variations (codecision part): first reading vote in the European Parliament on the Commission proposal

10 June 2008: Better Regulation of pharmaceuticals: Revision of the Variations Regulations: Commission delivers on cutting red tape

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The New Variation Regulation (Comitology proposal)

Comitology part – current status

1. Public Consultation (Start: 25 October 2007)
2. Outcome of the Public Consultation (14 January 2008): 48 written responses + discussion with Pharm Committee, HMA, NtA, CMD and Industry
3. First discussion of an incomplete draft of the EC (03 April 2008) in the Standing Committees (SC's)
4. Further SC's discussion on 02 June 2008
5. Final discussion and voting on 10 June 2008
6. Scrutiny process until 13 September 2008

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Scope of the new Variation Regulation

As currently

- ex-concertation/MRP/DCP
- following harmonisation (Article 30 and 31(1))

for **authorised** medicinal products

Outside:

- change of the MAH
- changes to **registered** homeopathic and traditional herbal medicinal product (despite they are elegible for the MRP/DCP)

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Key Item 2: Design space

Design space

- implementation of ICH Q8-Q10
- changes within the approved design space are no notifications or variations

Introduction

- as part of an initial marketing authorisation
- as a Type II Variation
  - ➢ new design space
  - ➢ change to an approved design space

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Key Item 3: „Do and Tell" (Type IA)

- (can be) implemented by the MAH before notification to CA
- reporting to CA either
  - – immediately (for defined Type IA eg change of address, …)
  - – within 12 months at the latest (no fixed date, ‚Annual Report')
  - – ‚Annual Report' alone or together with an immediate reporting

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Key Item 4: Two Key Definitions …

Grouping

what to place in one application

Worksharing

how to evaluate an application

➡ therefore worksharing on a grouped application is possible

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Key Item 4: Grouping

- **2-dimensional matrix**
  - – several changes to one MA
  - – identical change to several MA's
  - – (several identical changes to several MA)

  at the same time for the same MAH
- classification according to the highest level of the individual submission type
- **optional** for the MAH ⇨ all or nothing approach?
  No, as you submit an application, but CA grant a variation

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Key Item 4: Worksharing - (1)

- for „… several MA's owned by the same holder."
- for Type IB, Type II and grouped variations
- Coordination
  - Agency - if one central MA is included
  - CMD (h/v) - in all other cases
- Evaluation (‚reference authority')
  - Agency: Scientific Committees eg. CHMP
  - CMD: CA of a MS concerned, chosen by CMD considering recommendation by MAH

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Key Item 5: Worksharing - (2)

- Procedure
  - submission of application to all CA concerned
  - validation by ‚reference authority'
  - 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)
  - relevant authorities (concerned by the application) shall recognise the opinion of the ‚reference authority' within 30 days or raise PSRPH (resulting in a CMD or CHMP referral)

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Key Item 5: „Type IB by default" - (1)

- defined lists in classification Guideline for Type IA, II and line extensions (regularly amended by IB variations after Art. 5 procedure)
- unlisted changes are by definition Type IB

  but,

  if during the validation the CA consider a significant impact on quality, safety or efficacy, the application is considered a Type II variation

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„Type IB by default" - (2)

… cont.

alternative:

- MAH can ask CMD (national MA) or Agency (central MA) for a scientific recommendation on the classification of unlisted changes
- scientific recommendation within 45 days from CMD or Agency
- CMD and Agency shall cooperate and publish the scientific recommendations following deletion of commercial confidential informations (and this will effectively lead to an update of the Guidelines)

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Other items - (1)

- National implementation of SPC, PL and labelling after a Type II-Variation?
  - implicit approval within 30 days after submission of (high quality) translations
- How long should/could be the current stock on the market?
  - national issue
- Referrals
  - for Type II and Worksharing (but Article 35(2) of Directive 2001/83/EC, as amended is applicable)
  - only by NCA (not MAH!)

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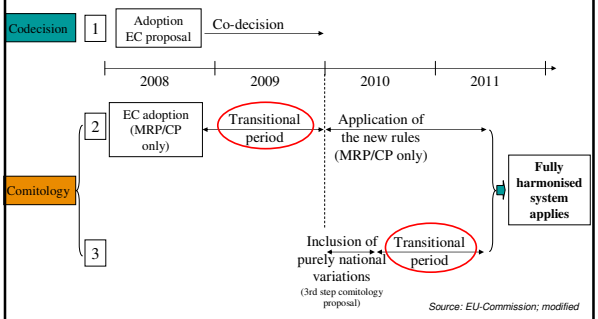
Other items - (2)

- Implementation
  - the current Variation Regulations shall continue to apply for valid notifications or pending variations
  - shall enter into force on the 20th day following publication
  - shall apply from <1 year after entry into force>, with the exception of Article 5 (*Recommendation on unforeseen variations*)



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Next Steps … - (1)

- Co-decision:
  - ongoing discussion in the Council
  - 1st reading finished in Parliament
- Comitology:
  - scrutiny procedure at EP until 13th September 2008
  - formal adoption by EC and publication
- Further work on other items:
  - Key Item 1
  - Fees (Council Regulation for the CP)

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Next Steps … - (2)

Guidelines

- Procedural Guideline Proposal
  - CMD (h+v) subgroup
  - EMEA
  - CxMP
- Classification Guideline Proposal
  - CMD (h + v)
  - EMEA
  - QWP
  - BWP
  - IWP

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Next Steps … - (3)

cont. **Guidelines**

- The WGs on the Procedural and the Classification Guideline Proposal are coordinated by the 'Variation Task Force':
  - EMEA
  - CHMP
  - CVMP
  - CMD (h)/(v)

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Next Steps … - (4)

cont. Guidelines

- The guidelines will be forwarded by the 'Variation Task Force' to the European Commission and thereafter for external consultation

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Conclusion

- Commission proposal is a big step into right direction
- Many aspects of the simple German system have been considered
- New variation system is expected to disburden the NCAs from huge workload with variation procedures
- NCAs will be involved in further development through Variation Subgroup and other Committees and working groups
- Classification and Procedural Guidelines should be finalized asap and well before implementation of the new system …

Thank you for your attention!

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List of Abbreviations

- CMS = Concerned Member State(s)
- CP = Centralized Procedure
- CR = Commission Regulation
- DCP = Decentralized Procedure
- MA = Marketing Authorisation
- MRP = Mutual Recognition Procedure
- NCA = National Competent Authority
- NtA = Notice to Applicants
- PIL = Patient Information Leaflet
- RMS = Reference Member State
- SPC = Summary of Product Characteristics