New Variation Regulation

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- Structure of the new system
- How it applies to national authorizations
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Background

Commission review project

- 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

Aim of the Review

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

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 authorisation 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, modified

The New Variation Regulation (Codecision proposal)

Co-decision part – 1

- This part extends the new rules to products authorised nationally ⇨ Council and EP must agree
- Adopted by the European Parliament October 22, 2008
- Council Decision still outstanding
- Provision for MS to continue to apply national provisions for variations to MAs granted before January 1, 1998

Co-decision part – 2

- New amending directive
  - currently draft for linguistic and formal review
  - publication in OJ expected shortly
  - transposition by MS into national law
  - applies 18 months after the date of entry into force
- New Chapter for national variations to be included within Variation Regulation by new comitology procedure

⇨ Full harmonisation expected late 2011/early 2012

Where to find published information?

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

27/10/08

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

On 22 October, the European Parliament (EP) has voted in first reading on the Commission proposal for a Directive amending Directive 2001/83/EC and Directive 2001/82/EC as regards variations to the terms of marketing authorisations. The proposal is part of a global revision of the legal framework on variations to make the overall system clearer, simpler and more flexible. This proposal in particular aims at amending the legal basis for the adoption of Community rules on variations in order harmonise those rules for all authorised medicines in the EU.
The final EP opinion has been adopted with a very large majority. The EP has endorsed the objectives and key elements of the Commission proposal and has introduced certain amendments. These include in particular the clarification that the implementing rules by the Commission should ensure simplification and the introduction of a possibility for Member States to continue applying national rules on variations to medicinal products fulfilling certain conditions. The EP's legislative resolution and the Commission proposal, after introduction of the EP amendments, can be found here.

This first reading opinion of the European Parliament paves the way for adoption of the text by the Council and the EP without a need for a second reading.

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

On 10 June 2008, the Member States have approved the new Commission Regulation on variations which will replace the existing Regulations (EC) No 1084/2003 and 1085/2003. The draft Regulation was put to vote at a joint meeting of the Standing Committee on Medicinal Products for Human Use and the Standing Committee for Veterinary Medicinal Products. Both Committees issued a favourable opinion by a very large majority.

The agreed text now enters a 3-months period of scrutiny by the European Parliament and Council (until 13 September 2008), before it can be formally adopted by the Commission and enters into force. For economic operators, the new rules will apply one year after entry into force, i.e. most likely around Q4 2009.

The text of the Regulation which was approved on 10 June 2008 is available here.

BG CS DA DE EL EN ES ET FI FR HU
IT LT LV MT NL PL PT RO SK SL SV

The New Variation Regulation (Comitology proposal)

Comitology part – current status

- Comitology:
  - technical changes agreed by MS experts in June 2008
  - scrutiny procedure at EP until September 13, 2008
  - adopted by EC, published December 12, 2008

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:EN:PDF

⇨ **Commission Regulation (EC) 1234/2008**

- entry into force on January 01, 2009
- applies from January 01, 2010

Structure of the new system

General structure

- Introduction
- Chapter I – General provisions
- Chapter II – Variations to MRP/DCP
- Chapter III – Variations to CP
- Chapter IV, sec. 1 – Special procedures
- Chapter IV, sec. 2 – Amendments to decision granting the MA and implementation
- Chapter V – final provisions
- Annex 1-5

Art. 1 - Scope

As currently

- ex-concertation/MRP/DCP and CP
- 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 eligible for the MRP/DCP)

Art. 2 - Definitions

- Minor variation type IA – minimal impact on quality, safety and efficacy
- Major variation type II – significant impact on quality, safety and efficacy
- Extension of a MA – listed in Annex I
- Minor variation type IB – neither type IA nor type II nor extension

Art. 3 – Classification ⇨ Annex II

Minor variations of type IA:

- purely administrative changes
- deletion of manufacturing sites
- minor changes to approved test procedures
- changes to comply with Pharmacopoeia
- changes in secondary packaging material
- tightening of specifications

Art. 3 – Classification ⇨ Annex II

Major variations of type II:

- variations related to indications
- significant changes in the SmPC
- changes outside range of approved specifications
- substantial changes of the manufacturing process of active substance or finished product
- changes in manufacturing or sites of the a.s. of biologicals
- introduction of or changes to a design space
- etc.

Art. 3 – Classification – type IB

Minor variation of type IB:

- no extension and not defined in Annex II ⇨ type IB by default
- may be upgraded to type II on request of the holder
- may be upgraded to type II on request of the member states (RMS in consultation with CMS/EMEA) when variation is regarded to have a significant impact on quality, safety and efficacy of the medicinal product

Art. 4 - Guidelines

Commission in consultation with MS, EMEA and interested parties shall draw up guidelines on:

- Details of the various categories of variations
- Operation of the procedures and documentation to be submitted

To be regularly updated taking into account

- scientific and technical progress
- recommendations on unforeseen variations (see Art. 5)

Art. 5 – Unforeseen variations

Art. 5 provides recommendation of CMD/EMEA on classification of a variation on request of MAH or MS:

- to be provided within 45 days
- to be consistent with Art. 4 guidelines
- Coherence of recommendations from EMEA/CMD(h+v)
- publication
- in force since January 1, 2009 but not applicable in the course of the current regulations
- guidances with timelines and application form already published http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_135_2009_Rev0_Feb09.pdf

Art. 6 – Revision of product information

- Where a variation leads to the revision of the summary of product characteristics, labelling or package leaflet, this revision shall be considered as part of that variation.

⇨ No separate procedure for SPC, PL and labelling

⇨ National translations to be submitted with application for type IA and type IB

⇨ Submission of only English PI for type II and extension with national phase after approval

Art. 7 – Grouping

- Type IA:
  - different type IAs for one MA
  - same type IA for different MAs of the same MAH
  - same type IA group for different MAs of the same MAH

  ⇨ also for annual reports!!!

- Other variations – predefined in Annex III
  - applying to one MA (**incl. different strengths and forms**)
  - handled according to the highest classification

  ⇨ or, as agreed with competent authority
  (recommended to consult RMS/EMEA in advance)

Art. 7 – Grouping – Annex III

- an extension with associated variations
- type II with consequential changes
- type IB with consequential minor variations
- administrative changes to SPC, PL and labelling
- ASMF, VAMF or PMF
- **improvement** of manufacturing process and quality
- quality of human pandemic influenza vaccine
- Further defined groups are variations to pharmacovigilance system, USR, class labelling, PSUR, post-authorisation study, specific obligations, specific procedures or conditions

Art. 8, 14 – Type IA notifications

- Introduction of „Do and Tell“
- Possibility for annual reporting system (= grouping) for all type IA notifications of one MA 12 months after implementation of first variation at the latest
- For changes requiring continuous supervision „immediate notifications“
- Timetable of 30 days

Art. 9, 15 – Type IB notifications

- 30 day procedure
- Notification with grounds in case of unfavourable opinion
- + 30 days for MAH for amended documentation
- + 30 days to finalise

⇨ Tell, Wait and Do

⇨ Procedure unchanged!

Art. 10, 16 – Type II procedures

- 60 days for RMS after positive validation to prepare AR and draft decision
  - reduction of timetable for safety issues
  - extension of timetable for indications
- clock stop for supplementary information
- finalisation 30 days after draft decision

⇨ Tell and Wait prior approval

⇨ Procedure unchanged!

Art. 12, 18, 21 – Human influenza vaccines

- As in current Regulations, special provisions apply
- Allows a rapid annual update

⇨ Procedure unchanged!

Art. 13 – Coordination group and arbitration

- In case of divergent decisions on Type II variations or worksharing based on PSRPH, MS can refer the matter to the CMD
  ⇨ no referral for type IA and type IB
  ⇨ no provision for MAH appeal

- Current referral guidance/best practice will apply

Art. 19 – Extensions of MA

- Extension shall be evaluated according to the same procedure as for the initial MA

- Extension may be granted a new MA or be included in the initial MA
  ⇨ national decision

Art. 20 - Worksharing

- Worksharing applies to type IB, type II and groupings of several MAs of the same holder ⇨ no extensions!
- Worksharing may contain MRP/DCP and CP
- Reference authority is EMEA if CP is part of the worksharing, MS if not (holder may give recommendation)
- Timetable in regulation – as type II
- CMD referral in case of divergent decisions

Art. 22, 24(5) – Urgent safety restrictions

- may be initiated by holder in case of risks
  ⇨ deemed accepted within 24 hours unless objections are raised
- may be imposed by RMS or Commission on the holder in case of risks
- variation to be submitted within 15 days following initiation of restriction
- USR to be implemented within agreed timeframe

⇨ No change in legislation but ⇨ Current guidance reviewed and updated in agreement with PhVWP

Art. 23, 24 – Granting and implementation

- Timelines for amendment to decision granting the MA are given for each procedure type
- **Implicit approval** of type II 30 days after receipt of necessary documentation
  new: also relevant for changes of the pharmaceutical dossier
  ⇨ wait 30 days before implementation
- Extensions may only be implemented after granting of MS or amended Commission Decision
- USR and safety changes are implemented as agreed between MAH and RMS

Art. 26 - Review

Commission shall review application of the Regulation by 01.01.2012 regarding

- classification of variations
- necessary amendments to Annexes I, II +V
- scientific and technical progress

Annexes I-V

Annex I	Extensions of marketing authorisations
Annex II	Classification of variations (IA + II)
Annex III	Cases for grouping variations referred to in Article 7(2)(b)
Annex IV	Elements to be submitted
Annex V	Part I – extension of type II timetable (indications) Part II –extension worksharing timetable (several veterinary aspects)

Annex IV –Elements to be submitted

- List of all MAs affected
- Description of all variations to be submitted (incl. implementation date for type IA)
- Necessary documents as listed in guideline
- Description of relation between variations for grouped variations
- Relevant fee for CP
- Relevant fee and list of CMS/RMS in MRP/DCP

Implication on national authorisations

Impact on national licences - 1

- After implementation the Co-decision part all national licences will be handled according to the European variation system
- ➢ harmonised legislation for all types of licences
- ➢ same aspects of variations are commonly handled in EU with same conditions and same procedures
- ➢ simplification especially for globally acting companies and for NCAs
  ⇨ only one system saves resources!

Impact on national licences - 2

- German specific procedural handling remains:

- Online variation applications still possible
- Grouping is part of the Regulation
- Unit for simplified procedures remains
- Electronic submission of information texts still mandatory
- Fees are national item
- etc.

Exemption of national licences

- After majority vote in the parliament for national applications licenced in accordance with Directive 2001/83/EC as amended before 1998 the national variation system may still apply
  ⇨decision of member states

➢ Not applicable where MA granted in another MS

➢ Positve aspects like annual reports, worksharing etc. will not apply for products exempted from the revised Variation Regulation

➢ Additional workload for validation unit

➢ Still different legal basis for different types of licences

? Applicable for the Nachzulassung?

? Change of § 29 AMG necessary?

Guideline for defining variation types

Art. 4-Guideline - Structure

- Structure:
  - common high level guideline with procedural and categorisation annexes
- Procedural Guideline Annex (I):
  - EMEA, CMD (h+v) subgroup and CxMP involved in preparation
  - common text as far as possible, procedural differences described
- Categorisation Annex (II):
  - EMEA, CMD (h + v), QWP, BWP and IWP involved in preparation
  - clarifies scope of some Annex II variations
  - provides guidance on classification of additional variations
  - covers quality as well as safety/efficacy aspects
  - provides examples of Type IB variations
  - provides relevant documentation for type IA notifications

Art. 4-Guideline – Variation Task Force

Variation Task Force:

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

Art. 4-Guideline - Categorisation Annex

- Introduces clarifying general principles
- Classification according to MA structure

I. Administrative changes

II. Quality changes

1. Active substance
2. Finished product
3. CEP/TSE/monographs
4. PMF/VAMF
5. Medical devices

III. Safety, Efficacy, Pharmacoviligance changes

Appendix PMF/VAMF specific changes

Structure as before – now incl. type II

26	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	Secondary packaging site	1, 2	1, 2, 3, 8	IA_{IN}
b)	Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8	IA_{IN}
c)	Site where any manufacturing operation(s) take place, except batch release and secondary packaging, for sterile medicinal products manufactured using a non standard terminal sterilisation method, and biological/ immunological medicinal products.			II
d)	Site where any manufacturing operation(s) take place, except batch-release, primary and secondary packaging, for non-sterile medicinal products.		1, 2, 3, 4, 5, 6, 7, 8	IB
e)	Site which requires an inspection			II
Conditions				
1.	Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.			
2.	Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).			
3.	Product concerned is not a sterile product.			
4.	Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.			
5.	Product concerned is not a biological/immunological medicinal product.			
Documentation				

Art. 4-Guideline – current status

- Procedural and Categorisation Guidelines have been published by the European Commission for external consultation until May 18, 2009
- Industry workshop for first comments took place with European Commission and Variation Task Force on April 20, 2009

Art. 4 – Guideline – main comments

- **Categorisation annex**:
  - categorisation of biologicals too conservative
  - changes concerning PhVS too conservative
  - guideline too complex
  - specific variations missing

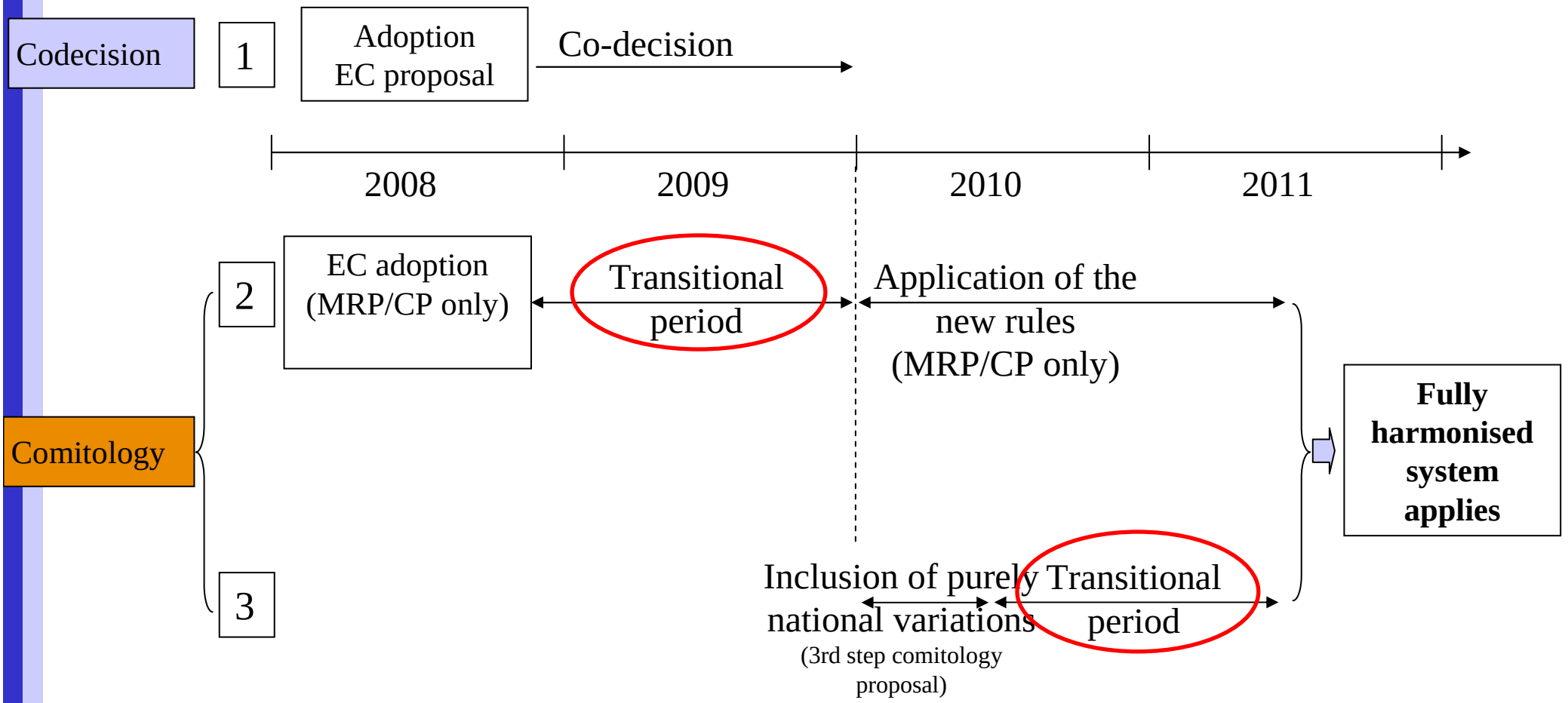
- **Procedural annex**:
  - advance information not practicable
  - consequences of rejected type IA notifications
  - type IB by default upgraded too frequently
  - all or nothing approach in grouping
  - product-specific changes excluded from grouping

Further Guidances

- CMD Best Practice Guides for the submission and processing of Variation in MRP/DCP will be updated according to the new Regulation and Guideline
- EMEA Post-authorisation procedural advice (PAG) will be updated according to the new Regulation and Guideline

Status of the consultation and procedure

Implementation Timetable



Source: EU-Commission; modified

Next steps - Regulation

- Co-decision:
  - for final adoption in the Council
  - 1st reading finished in Parliament
- Comitology:
  - public consultation of Guideline acc. to Art. 4 until May 18, 2009
  - 2nd Comitology procedure for introduction of national MAs into the Variation Regulation (after January 01, 2010 – implementing Co-decision)
- Further work on other items:
  - Fees (Council Regulation for the CP)

Next steps – Guideline and Guidances

- public consultation on Art. 4-Guideline until May 18, 2009
- internal adoption of procedures in EC
- further meeting of EC and Variation Task Force in June/July for agreement
- internal consultation in Commission
- Guidelines published by EC in November 2009
- Best practice guidances/PAG published afterwards

Conclusion

Conclusion

- Variation Regulation 1234/2008 is very welcome
- Many aspects of the simple German system have been considered and even exceeded
- New variation system is expected to disburden the NCAs and Industry from huge workload with variation procedures
- NCAs will be involved in further development of guidance documents through Variation Subgroup and other Committees and working groups
- Art. 4-Guideline and further guidance documents should be finalized asap and well before implementation of the new system

…

We look forward to further successful cooperation!!
Thank you for your attention

List of Abbreviations

- AMG = Arzneimittelgesetz (German Drug Law)
- CMD = Coordination Group for MRP and DCP
- CMS = Concerned Member State(s)
- CP = Centralized Procedure
- CR = Commission Regulation
- DCP = Decentralized Procedure
- MA = Marketing Authorisation
- MAH = Marketing Authorisation Holder
- MRP = Mutual Recognition Procedure
- NCA = National Competent Authority
- PAG = Post authorisation guidance (EMEA)
- PI = Product Information
- PIL = Patient Information Leaflet
- RMS = Reference Member State
- SPC = Summary of Product Characteristics