

The new EU Variations Legislation

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Industry Perspective

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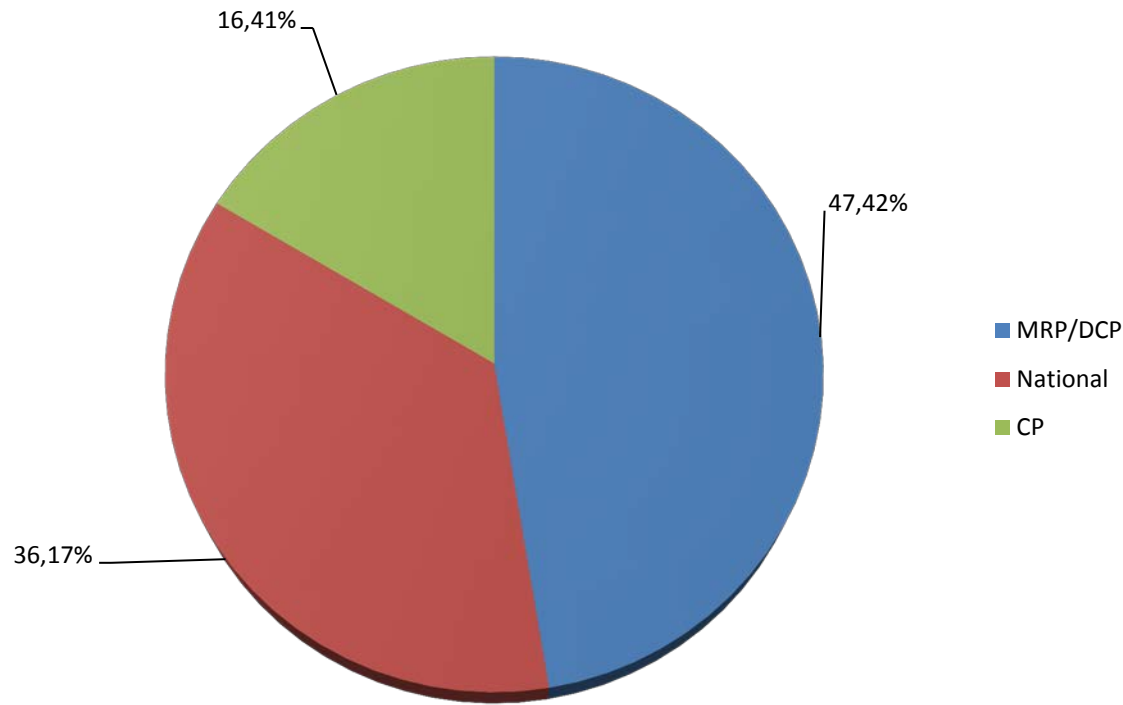
DGRA Annual Meeting, Bonn

Disclaimer

- I do not hold a Swiss bank account with dirty money
- I have never done money laundry in tax havens
- For all Bavarian colleagues: Preparation of all slides w/o employment of family members
- Tried hard to avoid missing citations (morbus Guttenbergiensis)
- The following slides represent the view of the author
- Anything I have forgotten to disclaim

Introduction

- RA perspective of a mid sized manufacturer of biological (mainly plasma derived) products (**37**)
- Portfolio (EU) by submission type:



Agenda

- Overview: Implementation of the new Variation Legislation 2005-2013
- Issues/Experiences with the new Variation Regulation
- Expectations after the inclusion of purely national licenses in the Variation regulation
- Better Regulation for biologicals?

The new variation legislation 2005-2013

Part of EC's "Better Regulation"

"The regulatory framework in which businesses operate is a key factor in their competitiveness, growth and employment performance. Therefore, a key objective of the European Union's Enterprise policy is to ensure that the **regulatory environment is simple and of high quality**. This is why "better regulation" is a centrepiece of the European Commission's "Partnership for Growth and Jobs" - the renewed "Lisbon Strategy" launched in spring 2005."*

* Taken from EC website (http://ec.europa.eu/health/better-regulation_en.htm)

Background of the new variation legislation

“Simplification of the regulatory environment for the benefit of European businesses and citizens

Progress achieved to date *(as of 2011/12):*

2008 - Review of the Variations Regulations

Revision of Regulation (EC) No 1085/2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use

The objective is to **reduce** the **administrative burden** for industry **by streamlining** the circumstances obliging industry to **file applications for variations** of human and veterinary medicinal products”.*

* Taken from EC website (http://ec.europa.eu/health/better-regulation_en.htm)

Background of the new variation legislation

Variations Regulations

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

Objectives:

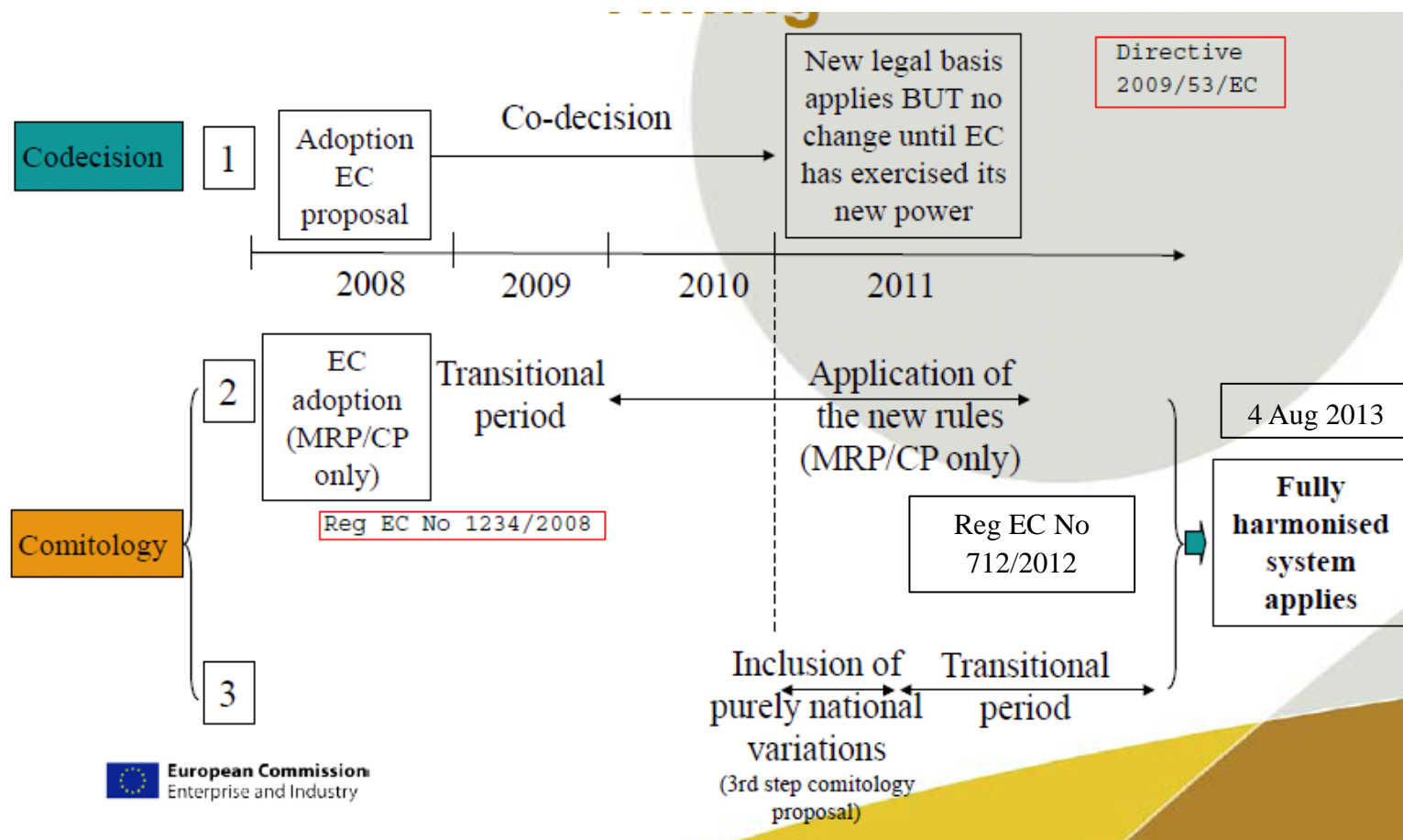
- Clearer, Simpler, More flexible
- Reduce administrative burden
- Adapt to ICH concepts
- Further harmonise

without compromising human and animal health



Martin Terberger, IPPC, Paris, 3 March 2009

Background of the new variation legislation



Martin Terberger, IPPC, Paris, 3 March 2009 – modified

Implementation – key steps

Item	Date	Effective/ deadline
Targeted consultation (industry associations and Member States competent authorities)	Oct 06	Jan 07
Public Consultation (co-decision part) of the revision of the Variations Regulations	10 July 07	21 Sept 07
Outcome summary of above (19 contributors)	3 Oct 07	
Public Consultation on the comitology part of the revision of the Variations Regulations, on the basis of two documents	25 Oct 07	4 Jan 08
Outcome summary of above (48 contributors)	14 Jan 08	
The Commission has adopted its 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 (codecision part)	4 Mar 08	

Implementation – key steps

Item	Date	Effective/ deadline
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	10 Jun 08	13 Sep 08
Commission Regulation (EC) No 1234/2008	24 Nov 08	12 Dec 08 (OJ) 1 Jan 09 (unforeseen var. recommendation) 1 Jan 10 (new system)
Directive 2009/53/EC of the European Parliament and of the Council amending... Directive 2001/83/EC (possibility for a MS to apply national variation system, but only for MA before 1 Jan 98 & single EU license)	18 June 09	30 June 09 (OJ) / 20 Jan 11

Implementation – key steps

Item	Date	Effective/ deadline
Public consultation: Implementation of the Variations Regulation: Guidelines on i) the operation of the variation procedures and ii) on the various categories	Feb 09	
Outcome summaries of above (i) 29 contributors, ii) 47 contributors	July 09	
Implementation of the Variations Regulation : Communication from the Commission - Guideline on the operation of the procedures - Guideline on the details of the various categories of variations	Draft Nov 09 Dec 09	1 Jan 10

Implementation – key steps

Item	Date	Effective/ deadline
<p>Public consultation paper Review of the variations regulation (1) The extension of the scope of the Variations Regulation to purely national MAs</p> <p>(2) The adjustment of some of the procedures with a view to focus resources of the authorities on variations with the most impact on public health</p> <p>(3) Some workability concerns identified.</p> <p>(4) Whether, in the light of the experience of last year, the procedure for the authorisation of vaccines in a pandemic setting should be amended</p>	21 Sept 11	22 Oct 11
Outcome summary of above (43 contributors)	Feb 12	

Implementation – key steps

Item	Date	Effective/ deadline
Commission Regulation (EC) No 712/2012 (main purpose: extend the application of the Variations Regulation to MAs granted at national level so that all marketing authorisations granted in the European Union (EU) are subject to the same rules)	3 Aug 12	4 Aug 12 (OJ) 2 Nov 12 (CP aspects) 4 Aug 13 (all MAs)
Public consultation paper - review of the variations guidelines on the details of the various categories of variations	June 12	15 July 12
Outcome summary of above (40 contributors)	Jan 13	

Implementation – key steps

Item	Date	Effective/ deadline
Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.	16 May 13	4 Aug 13

from http://ec.europa.eu/health/better-regulation-variations-regulations-developments_en.htm - modified

Issues – public consultations - example

- EC/DGE 2 public consultation papers, February 2009
 - Operational procedures
 - Detailed classification guideline
- 29/47 stakeholders responses, including PPTA
- 2 High level summaries DGE (2 pages)
- **No specific outcome comments from DGE**

Variation no.	Stakeholder No. <to be completed by DG ENTR>	Comment and Rationale; proposed changes <if changes to the wording are suggested, they should be highlighted using “track changes”>	Outcome <to be completed by DG ENTR>
9		Comments: A change of a supplier of a starting material/reagent that meets Eur. Pharmacopoeia criteria where there is no change in the specifications of a starting material/reagent used in the manufacturing process of the active substance should not require a type II variation just because it relates to a biological/immunological product.	

from PPTA response

Issues - Biologicals

- Workshop EC-Industry on 20. April 2009 → request for a specific workshop on biologicals as no substantial improvement/downgrading of type II variations was seen
 - Workshop for Biological Medicinal Products 23. July 2009 → no significant impact on final guidelines, e.g. PPTA: detailed annex for changes to biologicals allowing IB instead of type II

Issues with the implementation of the new Variation Regulations (1)

- **Late availability** of complete set of guidances and application forms (Dec 2009) → companies and authorities not well prepared for introduction in January 2010 → common learning curve ☺
→ clear improvement for 2013 revision ☺
- Purely **national MAs** not initially encompassed; however some MSs have introduced it, some with different timelines → **complicated transition phase**

A long way for purely national MAs.....



IMPLEMENTATION OF THE VARIATION REGULATION N° 1234/2008 IN EACH MEMBER STATE FOR MEDICINAL PRODUCTS AUTHORISED BY PURELY NATIONAL PROCEDURES

Doc. Ref.: CMDh/164/2010/Rev3
October 2012

It is reminded that it is not possible to combine nationally and European authorised products in the same variation, until the Variation Regulation is amended, allowing to apply the provisions to purely national products.

Will the variation regulation N° 1234/2008 be implemented from 1st January 2010 also for medicinal products authorized by purely national procedures?

	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HU	IE	IS	IT	LI	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK
No	X				X	X						X													X					
Yes		X	X	X				X	X				X			X						X				X		X	X	X
Yes, but different timelines							X			X	X			X	X			X		X	X		X	X			X			

Implementation of the Variation Regulation 1234/2008 in each MS for medicinal products authorised by purely national procedures

CMDh/164/2010/Rev3, October 2012

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- **Purely national MAs**

→ why took it so long (after acceptance of Directive 2009/53/EC) – 20 January 2011 deadline.

Simplicity? - Comparison EU versus (former) DE variation requirements

- Variations acc. to German medicinal product act (§ 29 AMG): „tell and do“ unless specifically defined as major change/new application requiring prior approval (implicit approval after 90 days) – **2 pages**
- Regulation EC No 1234/2008 – **18 pages**
 - Guidelines, explanatory notes, Q&As, examples, procedural advice
 - **239 pages** (status 2011/12)

Issues with the new Regulations

- **Grouping** not accepted, individual variations requested
- **Plasma Master File** (widely used, avoids submission of the same data for starting material in many dossiers; 2 step procedure; 1. scientific and technical evaluation by EMA/CHMP → (re-)certification. 2. Administrative 2nd step to amend it to respective MAs at national level.

*“A positive evaluation results in a certificate of compliance with Community legislation, which applies throughout the Community. As stated in Recitals (5) and (7) of Commission Directive 2003/63/EC, this certificate prevents from any subsequent reassessment of the corresponding PMF/VAMF data... Usually, variations to a PMF should not have an impact at the level of the concerned medicinal product(s). In this case, the Competent Authority should amend the dossier(s), simply by including the updated PMF data package and the corresponding certificate of compliance. This should be of **purely administrative nature.**” Guideline on PMF “second step”*

Issues – PMF second step

Before implementation of EC/1234/2008

- **Notification** (exceptions IT, ES, EL)
- **One submission** per country as **identical** documentation **package** containing:
 - One** cover letter
 - One** certificate including Annexes
 - One** expert statement
 - One** declaration of applicability
 - One** list of products
- **Workload**
 - Approx. **3 Working days**
 - One** employee centrally
- **Total costs**
 - ~ € 13.500**

After implementation of EC/1234/2008

- Classification as **Variation Type IA_{IN}**
- Variation implies change of each product dossiers: Approximately **100 eCTD sequences**
 - 65** cover letters
 - 65** application forms (including translations and proofs of payment)
 - Additional documentation as before
- **Workload:**
 - > 15 days**
 - > 10** employees involved, site/region
- **Total costs**
 - ~ € 100.000**

Issues – PMF second step

- Classification as Variation Type IA_{IN} remains also in future (post 4 August 2013)!



Burden for **authorities and industry**, cost increase for industry; **matter unresolved** despite several requests to CMDh, EMA, EC since May 2010.

Experiences – Fees - PMF variations

- **Variations to PMF:** 5 changes in one submission grouped as 1x type IA, 1x type IB, 3x type II. → 2010 EMA fees of **237,900€** → the same submission in 2008 **34,800€** due to umbrella approach, i.e. pay for the highest variation (1x type II).



EMA/EC responded to PPTA request adapted the cost structure for PMF variations as of October 2010 to previous procedure, i.e. here 1x type II with costs of **57,200€**



Not the same principle applied throughout

Issues

- Nationally required pre-payments: bureaucratic → extra efforts and delays, incompatible with speedy eSubmissions
- National gold plating, e.g. for MRP product RMS agreed application form (grouping) not accepted by one CMS → lengthy discussions/adaptions
- Higher overall fees

Interim evaluation of the new variation regulation

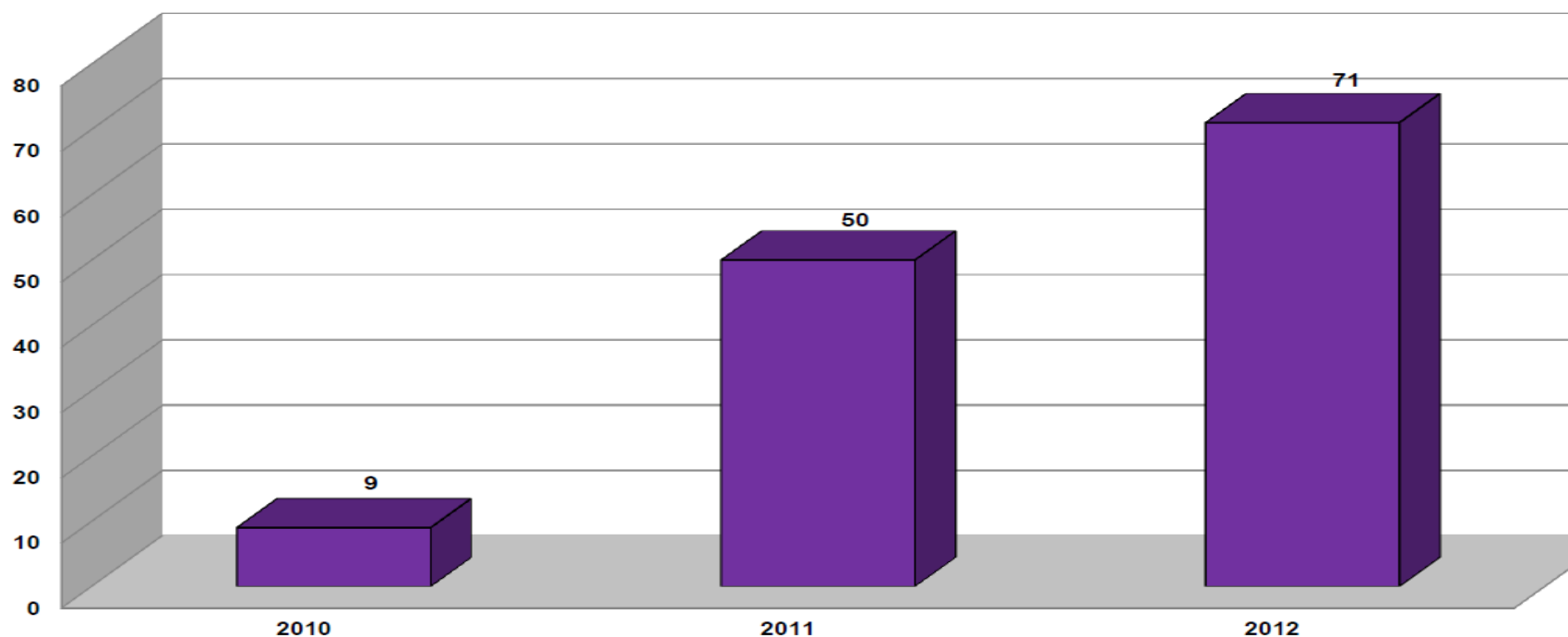
- All issues mentioned
- Not less type II variations required for biologicals
- Grouping possibilities less than former umbrella type approach
- Worksharing - no personal experience so far (missing inclusion of purely national MAs)
 - general experience apparently low (overleaf)

Worksharing



Implementation of variation regulation 1st January to 31st December 2012

Worksharing Procedures Finalised (2010-2012)



MRP/DCP & Art.29 referral procedures – Statistics for 2012

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Statistics/2012_Annual_Statistics_MRP-DCP___Art29___Art13.pdf

Expectations

- Full harmonisation of variation system including purely national MAs → highly welcome
 - benefit from worksharing possibility expected
 - defined clear timelines – to be adhered to!
however no definition of validation timelines except MRP/CP, Type IB (7 days)!!?
- no national gold plating to be tolerated! – feedback mechanism to EC?
- Continuous improvement program required - especially low hanging bureaucratic issues to be addressed

Proposals for further improvement (1)

- Pre-payment to certain health authorities → unnecessary bureaucracy/delays
- Fees: Discount for grouped variations due to reduced workload – or costs determined by actual working time spent, e.g. like PEI
- Remediate PMF situation, 2nd step issue as proposed by PPTA
- Continue discussion on downgrading certain variations from type II → IB variations for biologicals
- Grouping: more openness/flexibility

Proposals for further improvement (2)

- Possibility for non-critical product information changes as Type IB instead of Type II
- Clear feedback for public consultation comments
- After some experiences → defined validation timelines
- More concise guidelines – flow charts?

Better Regulation for biologicals/plasma derived products?

Objectives:

- Clearer, Simpler ☹️
- more flexible 😊
- adapt to ICH concepts 😊☹️
- reduce administrative burden ☹️
- further harmonization 😊
- simplification of legal framework 😊 😊 (lawyer's view)
- costs ☹️ ☹️

Final statement

Cetera Censeo
~~Carthaginem~~
Passum Secundum
Esse Delendam

Modified after the Roman elder
statesman Marcus Porcius Cato
Censorius



THANK YOU

