

EU-Variation System binding for national MA?

10th DGRA Annual Congress
Heading for a New Decade

Bonn, 17./18.06.2008

Susanne Winterscheid

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

Kurt-Georg-Kiesinger-Allee 3

53175 Bonn

Content

- Current situation
- Overview of the German variation system
- German position on Commission proposal
- Conclusion

Current situation MA ↔ variation

- National MA variations acc. to national law
- MRP/DCP variations acc. to CR 1084/2003
- CP variations acc. to CR 1085/2003

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

Current situation

- Continuously increasing numbers of variation applications
- Time and resources consuming process
- Variation Regulations are inefficient, overregulated and inflexible
- No satisfactory situation for NCAs and Applicant

Content

- Current situation
- Overview of the German variation system
- German position on Commission proposal
- Conclusion

Situation in DE

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

⇒ based on the legal self-responsibility of the MAH

Variations acc. to the German Drug Law § 29 AMG - (1)

	approval	
	§ 29 par. 2a AMG	
	Approval, if not refused within 3 months	
	<ul style="list-style-type: none"> • dosage • administration way • indications • deletion of adverse events, interactions, contraindications or warnings • pharmaceutical form (comparable) • change in gentechnological synthesis • Pack sizes 	

Variations acc. to the German Drug Law § 29 AMG - (2)

	approval	New application
	§ 29 par. 2a AMG	§ 29 par. 3 AMG
	Approval, if not refused within 3 months	invalid
	<ul style="list-style-type: none"> • dosage • administration way • indications • deletion of adverse events, interactions, contraindications or warnings • pharmaceutical form (comparable) • change in gentechnological synthesis • Pack sizes 	<ul style="list-style-type: none"> • active substance • pharmaceutical form (not comparable) • Extension of the indication outside of the currently approved therapeutic area • new gentechnological synthesis methods

Variations acc. to the German Drug Law § 29 AMG - (3)

notification	approval	New application
§ 29 par. 1-2 AMG	§ 29 par. 2a AMG	§ 29 par. 3 AMG
Immediately implemented with receipt in the BfArM	Approval, if not refused within 3 months	invalid
Examples: <ul style="list-style-type: none"> • MAH • Product name • Manufacturer • Manufacturing process • Excipients • Control methods • Stability <ul style="list-style-type: none"> • additional adverse events, interactions, contraindications or warnings • ... 	<ul style="list-style-type: none"> • dosage • administration way • indications • deletion of adverse events, interactions, contraindications or warnings • pharmaceutical form (comparable) • change in gentechnological synthesis • Pack sizes 	<ul style="list-style-type: none"> • active substance • pharmaceutical form (not comparable) • Extension of the indication outside of the currently approved therapeutic area • new gentechnological synthesis methods

Specifics of the national variation system in Germany (1)

- Non-related changes may be combined in one application
- Application form is not mandatory but highly recommended
- Online-variation system based on agreed European standards (NtA, Vol 2B) available since 04/2007

Specifics of the national variation system in Germany (2)

- Change in product name requires amendment of the MA and publication in the Federal Bulletin
- Electronic submission is mandatory for SPC, PL, labelling and overviews (AMG-EV)
- Notifications handled in separate unit „Simplified Procedures“

Specifics of the national variation system in Germany (3)

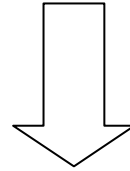
- Transfer of MA to a new legal entity is a simple notification procedure, no new MA will be issued
- Procedure start automatically with receipt of the variation application
- Implicit approval 3 months after receipt of application if no refusal is sent to the applicant – no clock stop, no request for supplementary information

Specifics of the national variation system in Germany (4)

No information concerning required documentation, but

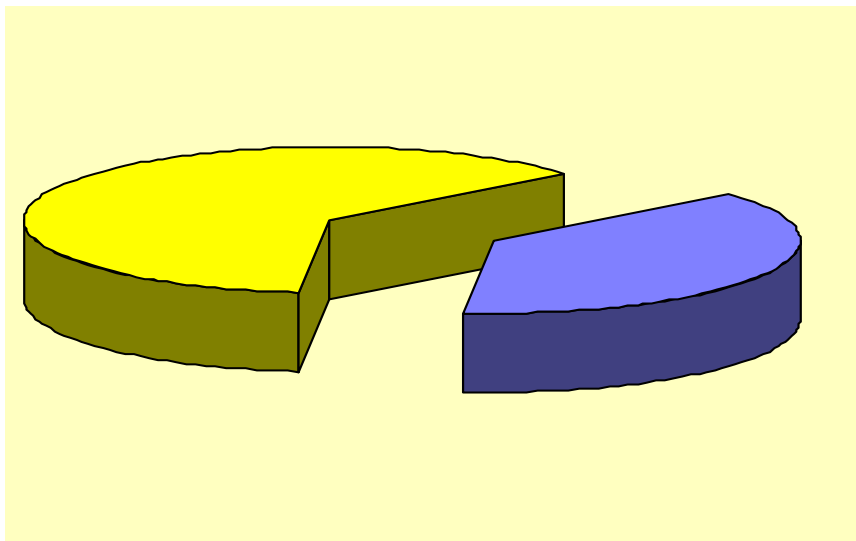
- Orientation to EU-Guidances, e.g.
 - SPC guideline
 - Guideline on dossier requirements for IA-/IB-Variations
 - Guideline on categorisation of Type II Variations vs. Extension Applications
 - Readability Guideline
 - Etc.

Submitted to the BfArM in 2007

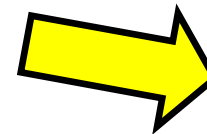


41733 Applications for Variations

National
(§ 29 AMG)
63 %

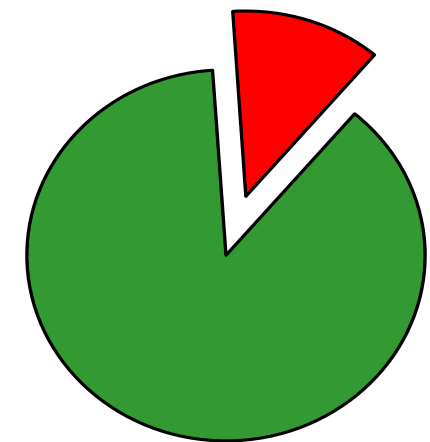


RMS 20 %



MR-Variations
(CR 1084/003)
37 %

**80 %
CMS**



15

Content

- Current situation
- Overview of the German variation system
- German position on Commission proposal
- Conclusion

Key Items of the review

1. Harmonisation of national and European legislation
2. Design Space (ICH Q8-Q10)
3. „Do and Tell“ and „Annual Report“
4. Worksharing
5. Type IB by default

General remarks

- Reduction of workload with constantly increasing variations is very welcome
- The proposed concept is basically endorsed as DE was always in favour of a simplification of the European variation system
- Simplification should be achieved for both, applicants and competent authorities
- Further aspects of simplification like electronic submission should be considered

Key Item 1 – Purely national authorisations

Harmonisation of national and EU legislation is still under discussion for human medicinal products in Germany due to the fact that existing German system is still easier to handle.

- Workload of the NCAs must not be increased.
- Basic Guidelines should be finalized before implementation of the regulation.

Key Item 2 – Design Space

Points for further discussion:

- Q8, Q9 and Q10 should all be finalized before
- Guidelines are missing
- Transfer to biologicals and special therapeutics (Phytotherapy, Homeopathy, Anthroposophy) should be verified

Key Item 3 – Do and Tell

Points for further discussion:

- Definition of IA and IA_N should be appropriately classified
- How to evaluate the annual report?
- Annual report must not lead to increase in workload of NCAs

Key Item 4 - Worksharing

Points for further discussion:

- Only for Type IB and Type II variations
- Line extensions should be excluded (MRP/DCP may be chosen)
- How to choose the right reference authority?
- Optional for the MAH (all or nothing approach?)
- No possibility for referral of the procedure

Key Item 5 – IB by default

Points for further discussion:

- Classification for major changes should be defined before implementation
- Biologicals should be excluded from this procedure – Type II by default should remain with possibility to downgrade in special cases
- No possibility of referral by NCA foreseen

Other items - Grouping

Points for further discussion:

- Line extensions should be excluded
- It should be clarified what to do, when only one change of a grouped variation is not acceptable – rejection of the whole group?

Other items - 1

- Introduction of generic definitions of variations is generally endorsed.
- Definition of extensions as variations is not acceptable – change or additional licence?
- Classification of variations in Guideline instead of Regulation Annex without involvement of NCAs is not acceptable – legally binding?
- Introduction of a mechanism regarding unclassified variations is endorsed – NCAs should be involved.
- National phase post-approval is not yet defined – implicit approval after 30 days?

Other Items - 2

- Clarification of deadlines for implementation is endorsed
- Referral of procedure should be possible for MAHs (Type IB and Type II) and NCAs (Type IB)
- Single regulatory text covering changes to all MAs (human and veterinary – CP and MRP/DCP) is very welcome – national authorisations?
- Annual report for administrative changes is desirable

Content

- Current situation
- Overview of the German variation system
- German position on Commission proposal
- Conclusion

Conclusion

- Commission proposal is a big step into the right direction
- Most proposed changes are supported
- Some aspects should be solved before implementation, e.g. Q8-Q10, electronic submission, etc.
- Line extensions should not be defined as variations
- NCAs should be involved in further development
- Guideline should be finalized before implementation and...

We look forward to further
successful cooperation!!

Thank you for your attention

List of Abbreviations

- AMG = Arzneimittelgesetz (German Drug Law)
- AMG-EV = Einreichungsverordnung
- 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