BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

Revision of the Variation Regulations (EC) 541/95 and 542/95

DGRA-Jahreskongress

19. - 20. 06. 2002

Bonn

Dr. Peter Bachmann
Bundesinstitut für Arzneimittel und Medizinprodukte
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

Disclaimer

All citations of the text of the proposed Regulation are based on a Draft.

As there is an ongoing discussion of the content and the exact wording of the Regulation, the citations may be not in all cases the most actual one.

Revision of the Variation Regulations

Why?

- to reduce the workload of the competent authorities (and industry)
- to built a variations system suitable for the enlargement of the EU

Revision of the Variation Regulations

Conditions

- **same regulatory framework** for variations in the Mutual Recognition and the Centralised Procedure
- the revision has to fit into the **existing legal framework**
  - Directive 2001/83/EC
  - Council Regulation (EC) No 2743/98

Directive 2001/83/EC

of 6 November 2001

Article 35(1)

...

The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

These arrangements shall include a **notification system or administration procedures concerning minor variations** and **define precisely the concept of ‚a minor variation‘**.

...

Revision of the Variation Regulations Basic Question - (1)

Does the content of the change need an evaluation or assessment?

- Yes ⟹ **major variation**
- No, because these are
  - administrative changes
  - simple changes, with no possible negative impact on the safety of the medicinal product

⟹ **notification system**

Revision of the Variation Regulations Basic Question - (2)

Problem:

Not the entire present list of Type I-Variations is suitable for a Notification Procedure

⇩

What to do with the „remains“?

second procedure for minor variations?

⇩

Council Regulation (EC) No 2743/98

Council Regulation (EC) No 2743/98
of 14 December 1998

Financial basis of the EMEA

Article 3

2. Variation

(a) Type I variation fee

(b) Type II variation fee

⇒ **two levels of fees possible**

1. full fee
2. ... may be halved for certain Type II variations ...

Revision of the Variation Regulations Basic Question - (3)

Council Regulation (EC) No 2743/98

⇩

Two Type II-Variation Procedures

↙ ↘

Implicit Approval
(Type IIA)
„present Type I“

Explicit Approval
(Type IIB)
„present Type II“

Revision of the Variation Regulations Proposed Structure (Draft 3)

The Regulation

- Urgent Safety Restriction
- Procedures for Type I, IIA and IIB

with

Annex I	(new Type I)
Annex II	(Type IIA)
Annex III	('line extention')

Revision of the Variation Regulations Where we are? - (1)

- Regulation 541/95 and 542/95 Draft 3
- Annex I Draft 6 (new Type I)

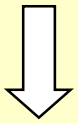
  Annex II Draft 1 (Type IIA)
  - for chemical defined medicinal products
  - biologicals, immunologicals and biotech medicinal products are still under discussion (EC, WP, NtA)
- Annex III Draft 3 ('line extention')
- Notification Form Draft 4

released for discussion to industry

Revision of the Variation Regulations Where we are? - (2)

March 2002 NtA-Meeting

- Discussion of the text of the Regulations
- Discussion of Annex III
- no discussion of Annex I and II
  - Type I = Annex I with 52 changes
  - Type IIA = Annex II with 41 changes
  - only for chemical defined active substances !!!



Revision of the Variation Regulations Where we are? - (3)

Participants (NL, UK, DE) of the NtA-Working Party are questioning the complexity of the new system and the impact of fees on the classification of variations

Decision of the NtA-Working Party:

an expert group shall try to solve the complexity

(Members: EU, EMEA, NL, IR, DE)

Revision of the Variation Regulations Where we are? - (4)

The Expert Group - Ideas

- merge list of Type I and Type IIA-Variations into one combined list (Guideline!!!, as new Annex???)
- combine different, but related variations under the same, general heading
- indicate for each particular case of such a ‚merged' variation, which condition(s), documentation and procedure would apply
- add all received comments to the ‚merged' variation

2 (+3 +1 +2). 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 for all types of pharmaceutical forms	1, 2	1, 2, 6	I (IA)
b. Primary packaging site			
1. Solid pharmaceutical forms, e.g. tablets and capsules	1, 2, 3	1, 2, 6	I (IA)
2. Semi-solid or liquid pharmaceutical forms	1, 2, 3	1, 2, 6	IIA (IB)
3. Liquid pharmaceutical forms (suspensions, emulsions)	1, 2, 3, 4	1, 2, 4, 6	IIA (IB)
c. All other manufacturing operations except batch release			
1. Modified release products or sterile formulations	1, 2, 4	1, 3, 6, 7, 8, 9	IIA (IB)
2. All other formulations	1, 2, 4	1, 3, 4, 6	I (IA)

Conditions:

1. satisfactory inspection in the last 3 years by an inspection service of one of the Member States of the EEA or of a country where an operational 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. 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.

- ~~supplier(s) of starting materials for the product remain(s) the same;~~
- ~~no change to the currently authorised manufacturing method or specification(s);~~

Revision of the Variation Regulations Where we are? - (5)

The Expert Group - Results

- drastic reduction of the total number of variations
- only one list to consult
- decision-tree approach
- removal of repetition of identical conditions & documentation for each related variation
- removal of inconsistencies between identical conditions & documentation presented under multiple related variations

Revision of the Variation Regulations Where we are? - (6)

The EU-Commission

- an unified Annex (Type I and Type IIA-Variations) is for the Regulation legally possible
- agreement on two Type I-Variations (Type IA and IB) and one Type II-Variation

current	proposed (Draft 3)	New Proposal (Draft 4)
	Type I	Type IA
Type I	Type IIA	Type IB
Type II	Type IIB	Type II

Revision of the Variation Regulations Where we are? - (7)

June 2002 NtA-Meeting

(17./18. 06.2002)

- agreement to the new proposal of the Regulation (Draft 4)
- adoption of the proposal from the Expert Group

Revision of the Variation Regulations Proposed Structure (Draft 4)

The Regulation

- Urgent Safety Restriction
- Procedures for Type IA, IB and II

with

‚new' Annex I (Type IA/IB)

‚new' Annex II ('line extention')

Revision of the Variation Regulations Where we are? - (8)

Ongoing Issues

- Expert Group will complete work on ‚new' Annex I - to be discussed at the next NtA-Meeting
- one Application Form for all types of variations
- proposal for a harmonized numbering system for mutual recognition and centralised variations - to be discussed
- new 'MRFG Best Practice Guides' for variations

Procedural Issues
Type IA and IB

Regulation 541/95 (Draft 4):

- Conditions of Annex I must be met
- Application to be send simultaneously to all Member States
- Fees have to be paid with the submission

Procedural Issues
Type IA - (1)

- Article 4 (5): Validation only be done by the RMS - no approval by the CMS

  "The national competent authority of the reference Member State shall acknowledge the validity of this notification within a maximum of 14 days following receipt of the notification and shall inform the other national competent authorities concerned and the marketing authorisation holder accordingly.
  ..."

„merged“ Annex I
Type IA - (2)

- 52 single entries
  - all administrative changes

    (change of the MAH (new legal entity) remains national)

  - all minor changes regarding the quality of the medicinal product eg
    - additional test procedures
    - tightening of limits
    - CoS
    - pack size of the finished product

„merged“ Annex I
Type IA - (3)

52. Change in pack size of the finished product

Condition to be fulfilled:

- the change only involves a change in the number of units (e.g. tablets, ampoules, etc.) in a pack;
- new pack size must be in the range of currently approved pack sizes;
- new pack size should be consistent with the posology and treatment duration as approved in the SPC;
- the primary packaging material remains the same.

Documentation to be submitted:

- *amendments to the relevant sections of parts II A, II C and II E;*
- *explanation as to why the new pack size is needed.*

Procedural Issues
Type IB - (1)

- automatic validation and start by the RMS

Article 5 (5):

"The national competent authority of the reference Member State shall acknowledge receipt of a valid application and shall start the procedure."

Procedural Issues
Type IB - (2)

- evaluation/approval is done by the RMS

Article 5 (6):

"If, within 30 days of the date of the start of the procedure, the national competent authority of the reference Member State has not sent the marketing authorisation holder its opinion provided for in paragraph 8, the variation applied for shall be deemed to have been accepted by all national competent authorities of the Member States concerned by the application."

Procedural Issues
Type IB - (3)

cont.

Article 5 (8):

"Where the national competent authority of the reference Member State is of the opinion that the application cannot be accepted ..."

Article 5 (6):

"The national competent authority of the reference Member State shall inform the other national competent authorities of the Member States concerned and the marketing authorisation holder to this effect."

Procedural Issues
Type IB - (4)

- no approval of the CMS is necessary

  Article 5 (7):

  "Each national competent authority concerned by the application for the variation shall, where necessary, amend the marketing authorisation which has been granted pursuant to Article 6 of Directive 2001/83/EC or Article 5 of Directive 2001/82/EC. "

- right of the MAH for Arbitration

  (Article 5 (9))

Procedural Issues
New Type II - (1)

All possible variations not listed in Annex I

Article 6 (5): FVAR within 60 days, but

"This period can be reduced to 30 days with regard to the urgency of the matter for variations related to safety issues.

This period can be extended to 90 days for variations concerning changes to or additions to therapeutic indications.

..."

Procedural Issues
New Type II - (2)

Article 6 (7): RMS is closing the procedure

Article 6 (8):

- no approval of the CMS is necessary, if the MA is not effected

  "Each national competent authority concerned by the application for the variation shall, where necessary, amend the marketing authorisation which has been granted pursuant to..."

Procedural Issues
New Type II - (3)

Article 6 (8):

- date of effectiveness for safety issues

  "For variations related to safety issues the national decisions shall take effect on the day agreed after discussion between the national competent authority of the reference Member State and the marketing authorisation holder in consultation with the other national competent authorities of the Member States concerned."

Article 6 (10): right of the MAH for Arbitration

‚Extension'
to an existing MA -(1)

Definition of ‚extension'

Article 3 (1c):

"An 'extension' of the marketing authorisation is a change as listed in Annex II to this Regulation."

‚Extension' to an existing MA -(2)

Annex II:

- an ‚extension' has to be granted

  "Certain changes to an existing marketing authorisation cannot be evaluated through a variation procedure but have to be evaluated using the 210 days evaluation procedure.

  ...

  An extention to or a modification of the existing marketing authorisation will have to be granted by the Community/national competent authorities."

‚Extension'
to an existing MA -(3)

Cont. Annex II:

"The Commission, in consultation with member states and interested parties, will draw up and publish detailed guidance on the documentation to be submitted."

Changes requiring an extension application

‚Extension'
to an existing MA -(4)

1. Changes to the active substance(s)

(i) replacement of the active substance(s) by a salt/ester complex/derivative (with the same therapeutic moiety) where the efficacy/safety are not significantly different

(ii) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer) where the efficacy/safety are not significantly different

‚Extension'
to an existing MA -(5)

Cont. 1. Changes to the active substance(s)

(iii) replacement of a biological substance or product of biotechnology with one of a different molecular structure where the efficacy/safety are not significantly different

(iv) modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety are not significantly different

(v) a new ligand or coupling mechanism for a radiopharmaceutical

‚Extension'
to an existing MA -(6)

2. Changes to strength, pharmaceutical form and route of administration

(i) change in bioavailabiliy

(ii) change of pharmokinetics e.g. change in rate of release

(iii) change or addition of a new strength

(iv) change or addition of a new pharmaceutical form

(v) addition of a new route of administration

‚Extension'
to an existing MA -(7)

3. Other changes specific to veterinary medicinal products to be administered to food-producing animals

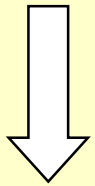
addition of target species

‚Extension'
to an existing MA -(8)

- Changes to the therapeutic indications:

DELETED

no item of Annex II



- Article 7 (5):

  therapeutic indications as Type IIB-Variation
- new full application for a MA („List B - Status")

Summary
(1)

- Type I A and Type I B-Variations are in the hands of the RMS
- a closed procedure doesn‘t need national approval, as long as the MA (= SPC ?) is not changed
- change of/additional therapeutic indications as Type II-Variation/New Full Application
- Definition of ‚extension‘ as change to an existing marketing authorisation

Summary
(2)

New Variation classification

	Procedure	Timeframe	Definition
Type I A	Notification	max. 14 days	Annex I
Type I B	Approval	‚old Type I'	Annex I
Type II	Approval	‚old Type II'	-
Extension	Authorisation	see Directive	Annex II