New Variations Regulation – "Quality Related Changes"

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Overview of presentation

- Regulation
- Annexes
- Classification Guideline
- Experience
- Guidance
- Summary

Background to changes

Commission Regulations (EC) 1084 & 1085/2003
(CP, MRP products – not nationally approved)

Considerable burden for industry and authorities (large number of variations)

Commission: Review project launched in 2006
"Better Regulation"

Objectives:

- Clearer, simpler, more flexible
- Reduce administrative burden
- Adapt to ICH concepts (Q8, Q9, Q10)
- Further harmonise handling of variations in EU

« *without compromising human and animal health* »

European Variations System - Evolution

1995 1998 2003 2006 2007 2008 2009 2010 2011 2012

New system developed

541/95
542/95

1146/98
1147/98

1084/2003
1085/2003

1234/2008 (European Regulations)

Type I
Type II (default)

Type I
Type II (default)

Type IA – “Tell and do”
Type IB
Type II (default)

Type IA – “Do and Tell”
Type IB (Default)
Type II

Effective

New Variation Regulation (1234/2008)

Annexes

I - Extensions

II - Classification of variations (IA and II) (High Level)

III – Grouping examples

IV – What should be submitted

V – Type II – 90 day procedure e.g. Change to or addition of therapeutic indication

Extensions of marketing authorisations

1. Changes to the active substance(s):

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

(b) 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 characteristics are not significantly different;

(c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of:
— changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;
— replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;
— replacement of a strain for a veterinary vaccine against equine influenza;

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

(e) a new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different;

(f) change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different.

Extensions of marketing authorisations

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

(a) change of bioavailability;
(b) change of pharmacokinetics e.g. change in rate of release;
(c) change or addition of a new strength/potency;
(d) change or addition of a new pharmaceutical form;
(e) change or addition of a new route of administration.

3. Other changes specific to veterinary medicinal products to be administered to food-producing animals: change or addition of target species.

ANNEX II – “HIGH LEVEL” Classification

Type IA – section 1

c) variations related to *minor* changes to an approved physico-chemical test procedure ……..

d) variations related to the specifications of the active substance or of an excipient in order to *comply with an update of the relevant monograph* of the European Pharmacopeia or of a national pharmacopoeia of a Member State ……..

f) variations related to the *tightening of specification limits*, where the change is *not a consequence of a commitment* from a previous assessment …… and does *not result from unexpected events* during manufacture.

ANNEX II – “HIGH LEVEL” Classification

Type II – section 2

b) variations related to *significant modifications* of the summary product characteristics due in particular to *new quality*, pre-clinical, clinical or pharmacovigilance findings;

c) variations related to *changes outside the range* of approved specifications, limits or acceptance criteria.

d) variations related to *substantial changes* to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which *may have a significant impact on the quality, safety or efficacy* of the medicinal product.

Regulation - Classification Rules

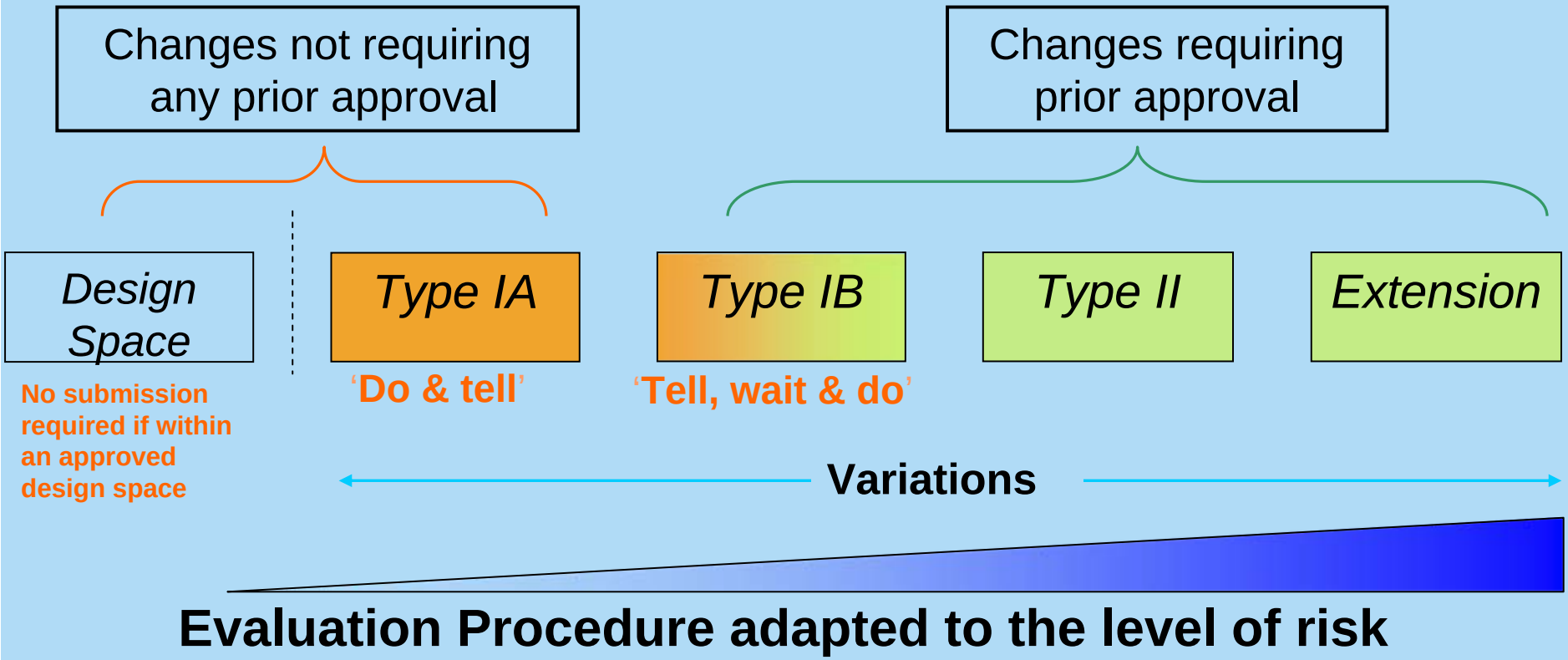
- Type IA and Type II pre-defined (high-level) in Annex II
- Extensions pre-defined in Annex I
- Unlisted variations = **Type IB by default**, with option for
  - MAH to submit as Type II
  - Auth. to require Type II at validation *(safeguard-clause)*

Classification Guideline (Key document)

- Type IA – conditions and documentation requirements fully defined (30 days)
- Type IA - IA/IA_{IN} – appropriately identified
- Type II – changes defined (*no documentation requirements) (30, 60, 90 days)
- Type IB – EXAMPLES defined with documentation requirements (no conditions) (30 days, except worksharing) (*facilitate submission & validation, ensure consistency, Avoid Art. 5*)
- Includes **Quality** + **Safety/Efficacy/PhVig** variations
  Appendix: specific changes to PMF & VAMF
- Regulation foresees regular updating

(* exception relates to Design Space categories)

Summary - Types of Variations



Guideline structure

TOPIC / SCOPE OF CHANGES	VARIATION	Page
A. ADMINISTRATIVE CHANGES	1-7	**5**
B. QUALITY CHANGES		**9**
I. Active Substance		**9**
a) Manufacture	1-5	9
b) Control of active substance	1-2	15
c) Container closure system	1-3	18
d) Stability	1	21
e) Design Space	1-3	23
II. Finished Product		**25**
a) Description and composition	1-6	25
b) Manufacture	1-5	31
c) Control of excipients	1-4	40
d) Control of finished product	1-3	44
e) Container closure system	1-7	47
f) Stability	1	54
g) Design Space	1-3	56

Guideline structure

III. CEP/TSE/monographs	1-2	**58**
IV. Medical Devices	1-3	**61**
V. Changes to a marketing authorisation resulting from other regulatory procedures		**64**
a) PMF/VAMF	1-2	64
b) Referral	1	66
c) Change management protocol	1	67
C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES		**68**
I. Human and Veterinary medicinal products	1-9	68
II. Veterinary medicinal product – specific changes	1-6	73
D. PMF / VAMF	1-23	**75**

Example – Efficacy/Safety

C.I.4 Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

C.I.6 Change(s) to therapeutic indication(s)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition of a new therapeutic indication or modification of an approved one			II
b) Deletion of a therapeutic indication			IB
Note: Where the addition or modification of a therapeutic indication takes place in the context of the implementation of the outcome of a referral procedure or of changes to the product information of a generic/hybrid/biosimilar product following assessment of the same change for the reference product, variations C.I.1 and C.I.2 apply, respectively.			

Example – finished product manufacturer

B.II.b) Manufacture

B.II.b.1 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	1,3, 8	IA_{IN}
b) Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IA_{IN}
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products.			II
d) Site which requires an initial or product specific inspection			II
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.		1, 2, 3, 4, 5, 6, 7, 8, 9	IB
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products manufactured using an aseptic method excluding biological/ immunological medicinal products.		1, 2, 3, 4, 5, 7, 8	IB

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.

IA

Type II biological/immunological

Examples (IB)

Example – Batch release/QC

B.II.b.2 Change to batch release arrangements and quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Replacement or addition of a site where batch control/testing takes place	2, 3, 4	1, 2, 5	IA
b) Replacement or addition of a manufacturer responsible for batch release			
1. Not including batch control/testing	1, 2	1, 2, 3, 4, 5	IA_{IN}
2. Including batch control/testing	1, 2, 3, 4	1, 2, 3, 4, 5	IA_{IN}
3. Including batch control/testing for a biological/immunological product and one of the test methods performed at that site is a biological / immunological / immunochemical method.			II

Annual

Conditions

1. The manufacturer responsible for batch release must be located within the EEA.
2. The site is appropriately authorised.
3. The product is not a biological/immunological medicinal product.
4. Method transfer from the old to the new site or new test laboratory has been successfully completed.

Example – finished product manufacture

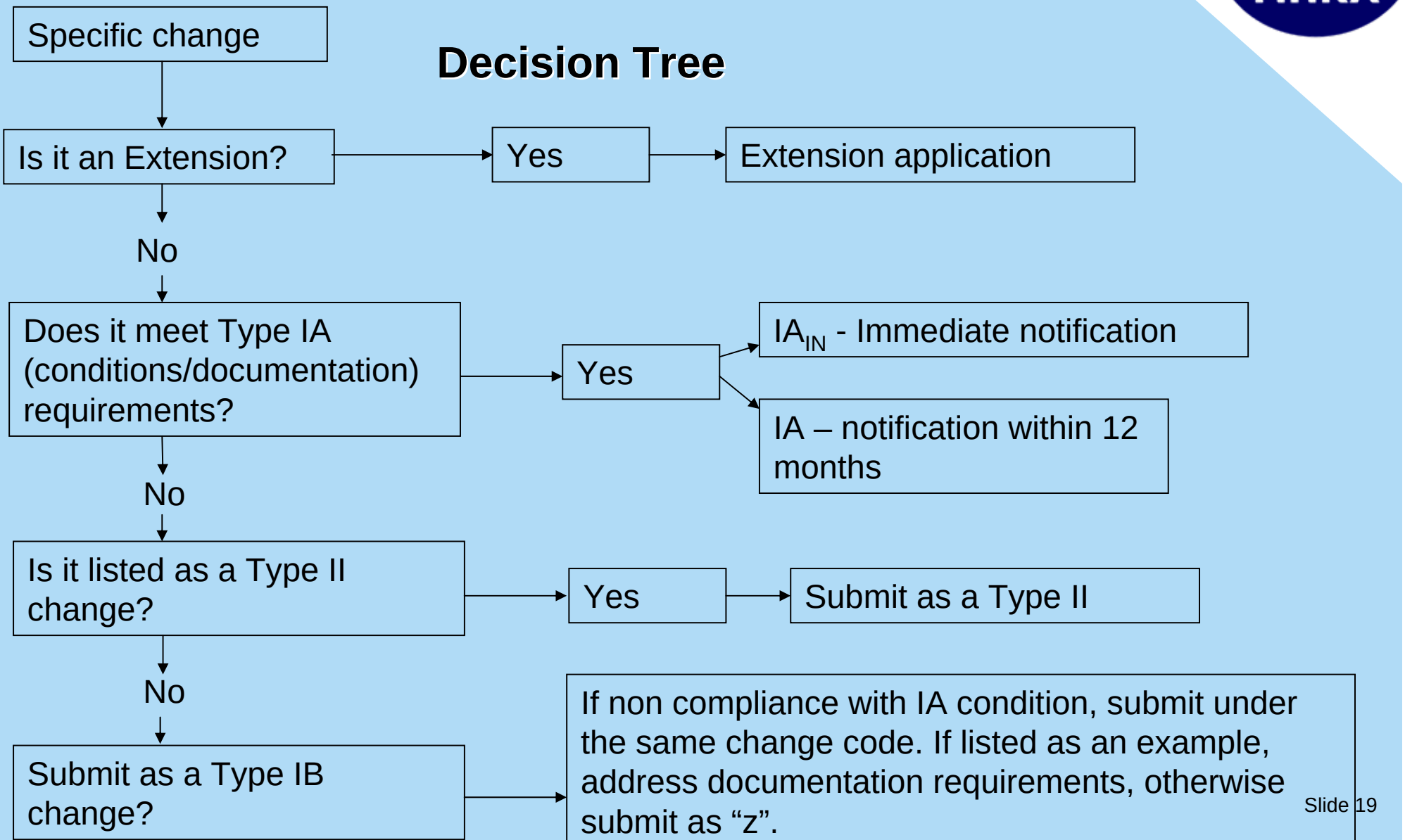
B.II.b.3 Change in the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions.	1, 2, 3, 4, 5, 6, 7	1, 3, 4, 6, 7, 8	IA
b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			II
c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability.			II
d) Introduction of a non-standard terminal sterilisation method			II
e) Introduction or increase in the overage that is used for the active substance			II
f) Minor change in the manufacturing process of an aqueous oral suspension.		1, 2, 4, 6, 7, 8	IB

Conditions

1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.
2. The product concerned is not a biological /immunological or herbal medicinal product.
3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.
4. The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls.
5. The specifications of the finished product or intermediates are unchanged.
6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

New system – classification guideline

Decision Tree



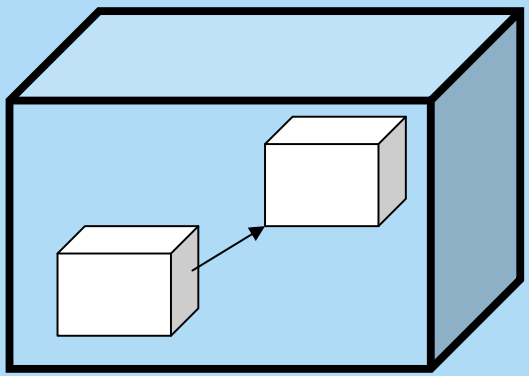
“z” category change in application form

	B.I.a.2	Changes in the manufacturing process of the active substance		Procedure type		
	☐	a)	Minor change in the manufacturing process of the active substance, except changes referred to in c), d) and e) below	IA ☐	IB[9] ☐	**Implement. Date:**
	☐	b)	Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.	II		
	☐	c)	The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol.	II		
	☐	d)	The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production.	II		
	☐	e)	Minor change to the restricted part of an Active Substance Master File.	II		
	☐	**z)**	**Other variation**	☐ IA ☐ IB ☐ II		☐ **Art 5**

ICH Q8/Q9/Q10

Design Space

- Any movement within approved Design Space (No variation)



- Introduction of new or extension of existing Design Space (Type II)

Post Approval Change Management Protocol

New concept introduced in EU through the Variations Classification Guideline

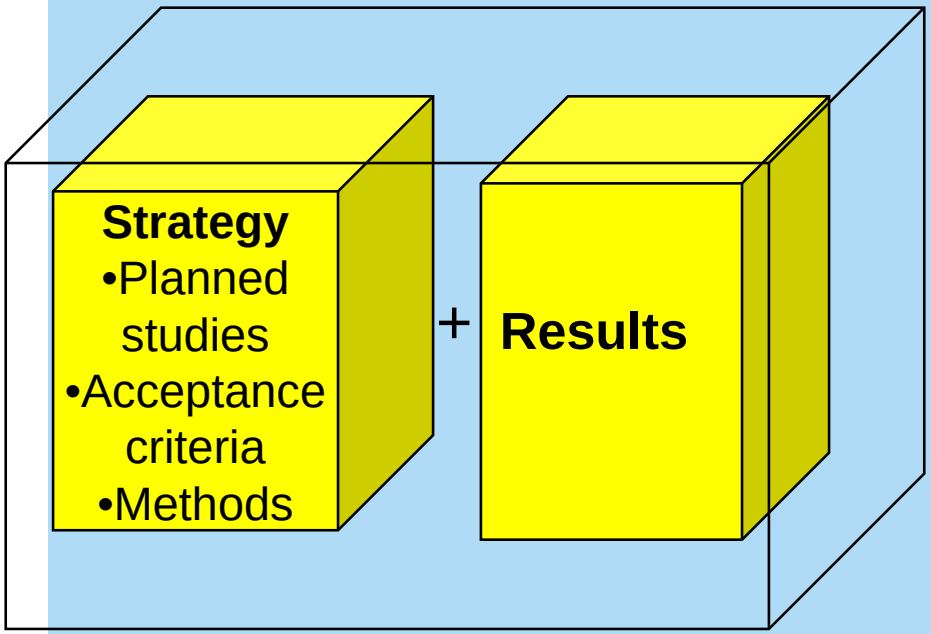
A change management protocol **describes specific changes that the MAH would like to implement during the lifecycle** of the product and how these would be prepared and verified**.**

It is a **step-wise approach** in the assessment of changes that facilitates their implementation post-approval

Aim: To facilitate the management of changes post approval. It's a means of the regulatory simplification and flexibility advocated by the new Variations Regulation

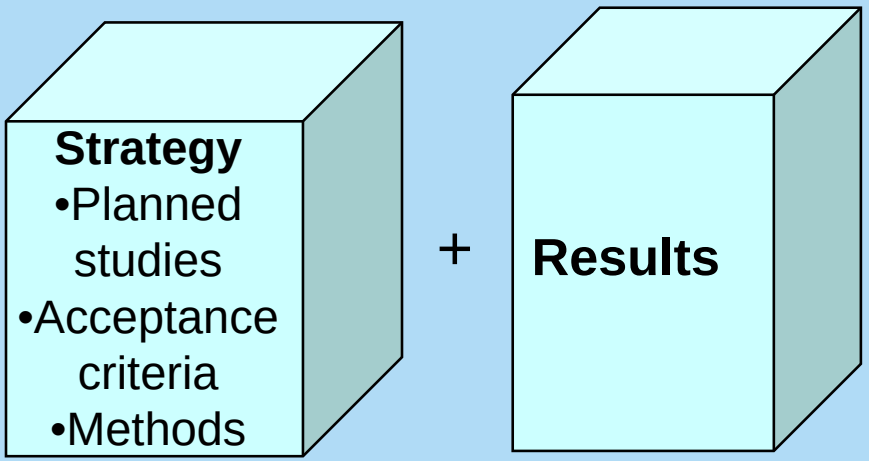
They are applicable both to Chemical and Biologicals

Post Approval Change Management Protocols



Standard approach

Evaluation of a proposed variation as a 'whole' (Strategy + Results)



Early Step 1:

Submission of a Protocol

Type II Variation or part of original MA

Quick Step 2:

Implementation of the change

Type IA_{IN} or IB Variation

Variation classification guideline - Finished Product (First step) (B.II.g)

B.II.g.2 Introduction of a post approval change management protocol related to the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	II

Documentation

1. Detailed description for the proposed change.
2. Change management protocol related to the finished product

B.II.g.3 Deletion of an approved change management protocol related to the finish product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}

Conditions

1. The deletion of the approved change management protocol related to the finish product is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol.

Documentation

1. Justification for the proposed deletion.

Variation classification guideline - Second step – implementation (B.V.c)

B.V.c) *Change management protocol*

B.V.c.1 Update of the quality dossier to implement changes, requested by the EMEA/National Competent Authority, following assessment of a change management protocol	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The implementation of the change requires no further supportive data	1	1, 2, 4	IA_{IN}
b) The implementation of the change requires further supportive data		1, 2, 3, 4	IB
c) Implementation of a change for a biological/immunological medicinal product		1, 2, 3, 4, 5	IB

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.

Documentation

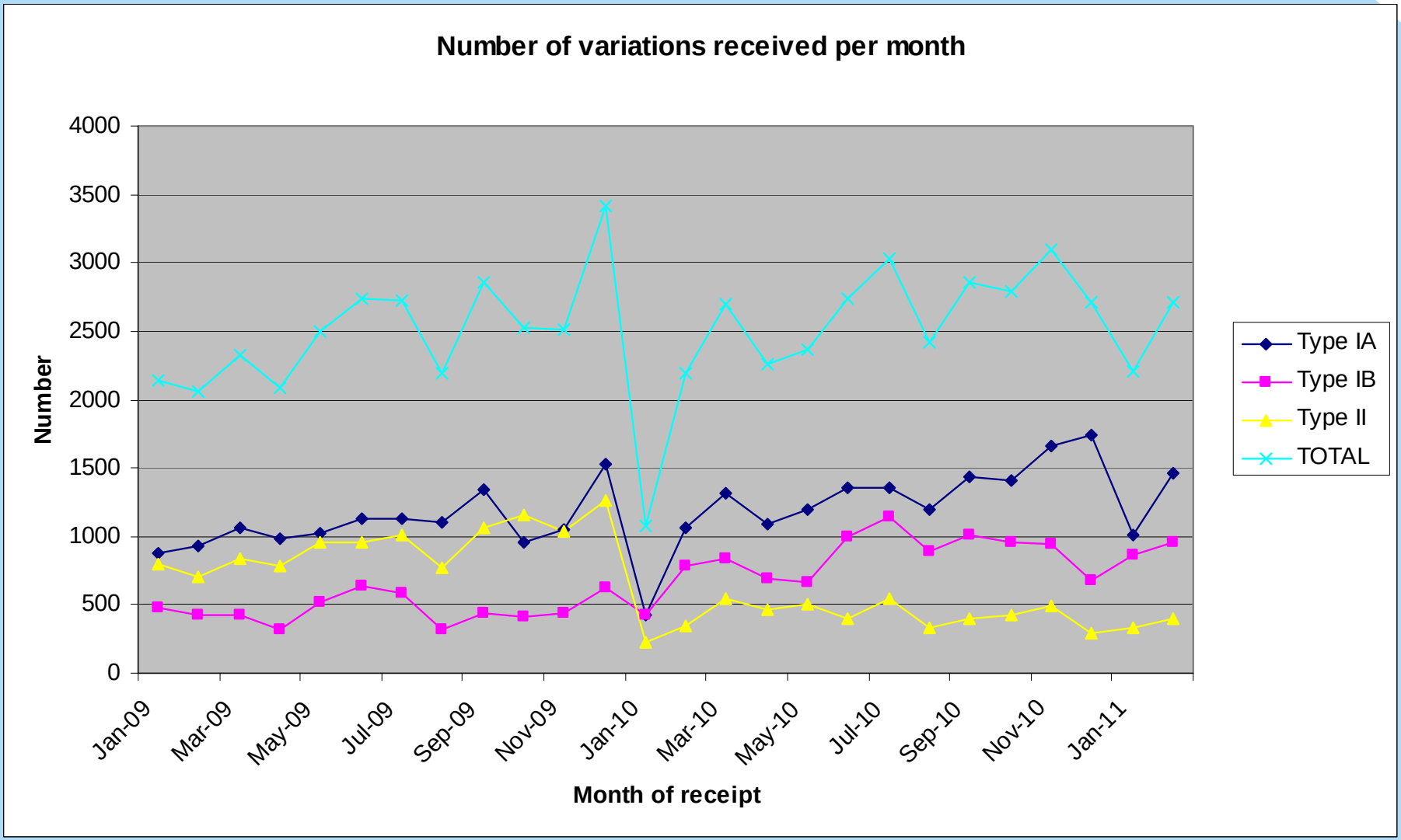
1. Reference to the approved change management protocol.
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.
3. Results of the studies performed in accordance with the approved change management protocol.
4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
5. Copy of approved specifications of the active substance or the finished product.

IA_{IN}

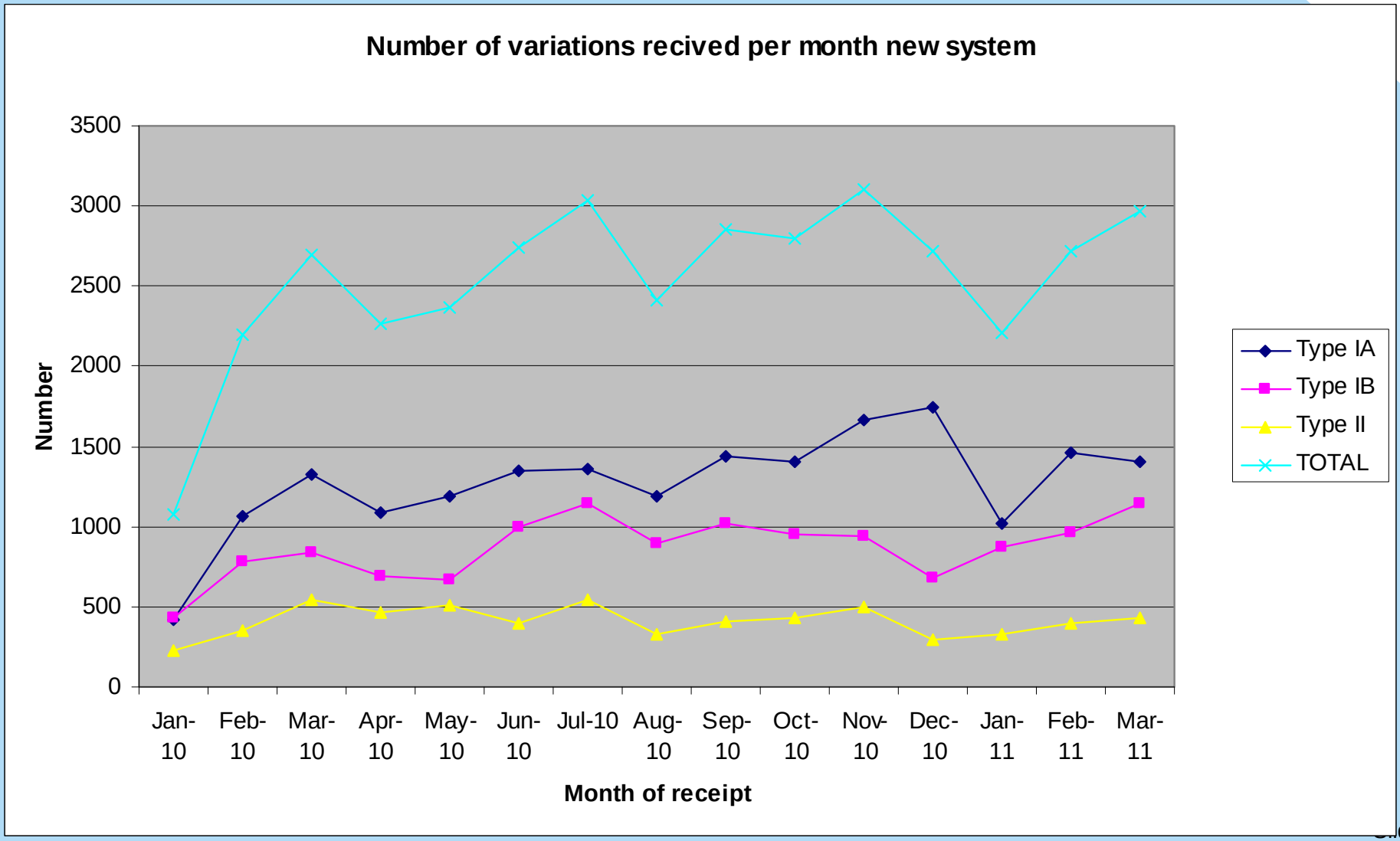
IB (Biological)

MHRA - EXPERIENCE TO DATE

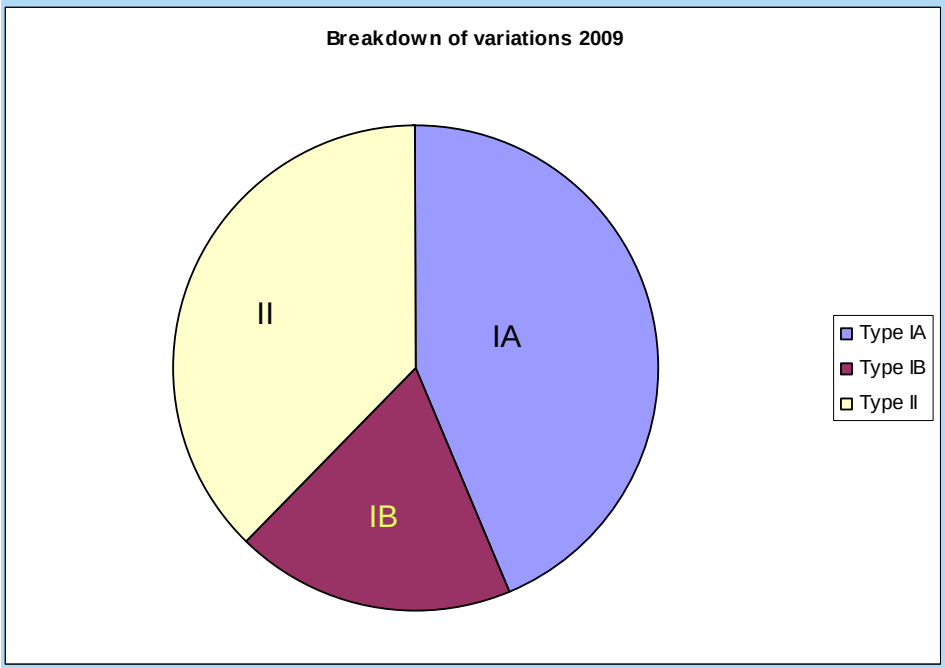
MA Variations in the UK (all procedures)

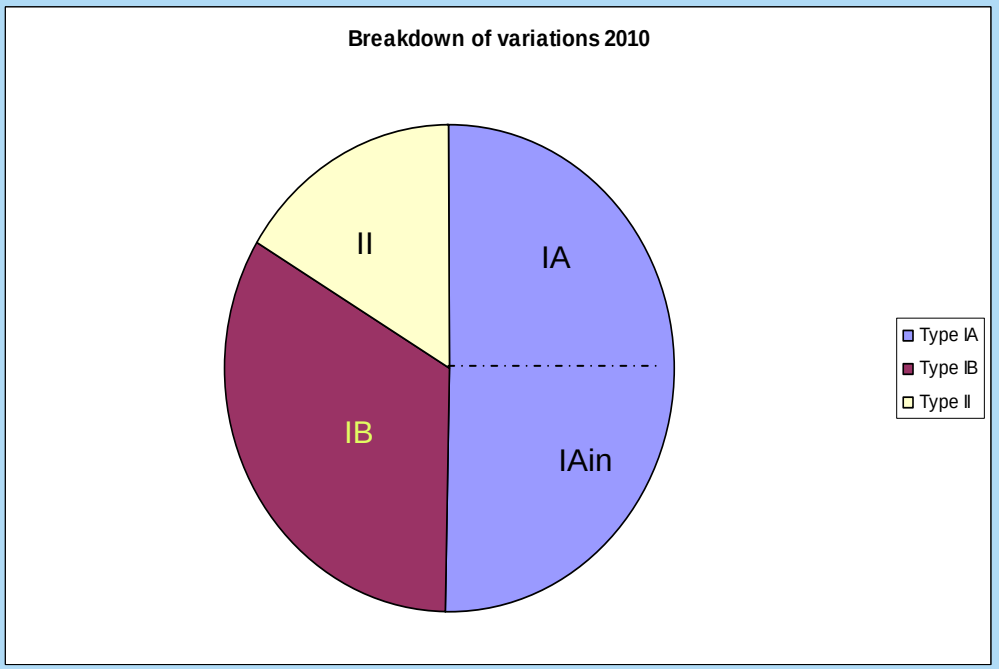


MA Variations in the UK (all procedures – 2010)



UK variations – comparative breakdown old/new system





Most common Type IA variations

Change Code	%	Description	Notification
A7	16.3	Site deletions	A
A1	12.5	Change to name/address of MA holder	IN
B.III.I.A.2	9.3	Update of CEP for active substance	A
B.II.B.2.A	6.1	Finished product – QC testing	A
B.II.B.I.A	6.1	Finished product - secondary packaging	IN
B.III.I.A.3	5.2	New CEP for active substance	IN
C.I.9.h	4.4	DDPS update (other)	A
B.II.B.2.B.1	4.2	Finished product - Batch release (no testing)	IN
A.5.A	3.5	Change in name of batch release site	IN
B.II.B.I.B	3.1	Finished product - primary packaging	IN
A.5.B	3.0	Finished product manufacturer name	A
A.4	3.0	Active substance manufacturer name	A
	76.7		

Most common Type IB variations

Code	%	Description
C.I.3.A	**26.2**	**Implementation of agreed SmPC wording changes**
A.2.B	11.5	Change in product name
B.II.B.I.E	6.3	New finished product manufacturer (non sterile)
C.1.2.A	**6.1**	**SmPC changes linked to reference product (no new data)**
B.II.D.2.D	4.6	Change of finished product test procedure
C.I.Z	**4.1**	**SmPC change by default**
B.II.B.I.Z	4.1	Change of finished product manufacturer (other)
C.I.8.B	**3.2**	**New DDPS (previously assessed)**
B.II.F.1.B.1	3.1	Shelf life extension
B.I.B.2.E	2.6	Active substance test procedure
B.I.D.I.A.I.4	2.1	Active substance retest period
B.I.A.1.Z	1.8	Active substance manufacturer
	75.7	

Most common Type II variations

Code	%	Description
C.I.4	**38.0**	**Significant changes of SmPC**
C.I.3.B	**11.1**	**Requested changes supported by additional data**
B.II.D.I.E	5.3	Relaxation of finished product specifications
C.I.Z	**4.7**	**Submitted by applicant by choice**
C.I.2.B	**3.6**	**SmPC changes linked to reference product (extra data)**
B.I.A.I.B	3.6	New active substance manufacturer (ASMF)
C.I.8.A	**3.5**	**New DDPS**
B.I.B.I.F	2.2	Relaxation of active substance specification
B.I.B.2.E	1.8	Test procedure - biological
B.II.B.3.B	1.5	Substantial change to the method of manufacture of the finished product
	75.3	

Sources of information/guidance

Notice to Applicants

http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

Final classification guideline
Application form

EMA

http://www.ema.europa.eu/pdfs/human/regaffair/4040410en.pdf

Post-authorisation procedural advice
Quality Working Party

Sources of information/guidance

CMD

http://www.hma.eu/96.html

- **Best Practice Guides**
- **Guidance for completion of application form**
- **Questions and Answers**
- **Acceptable and non acceptable groupings**

Regulatory Authority websites

MHRA

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/Variationstolicences/index.htm

Summary

Changes to the classification of variations are very significant in the Quality area – should benefit all

Future

- Something to build on
- System will evolve
- Expectation that the guideline will be regularly updated (flexibility)
    - Experience
    - New recommendations (Article 5)
    - New scientific developments

Any Questions?