Classification
Quality Variations for Biologics

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Principle

Extension

Type IA: "Do and tell"

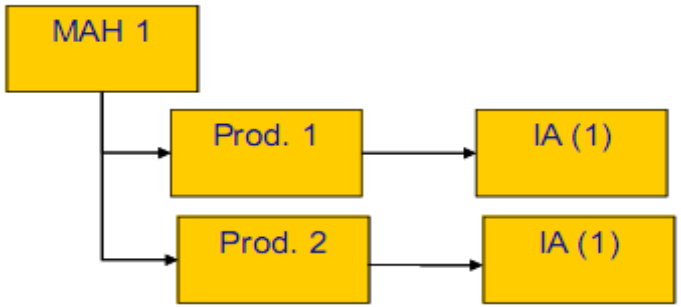
Type IB: "Tell, Wait and Do"

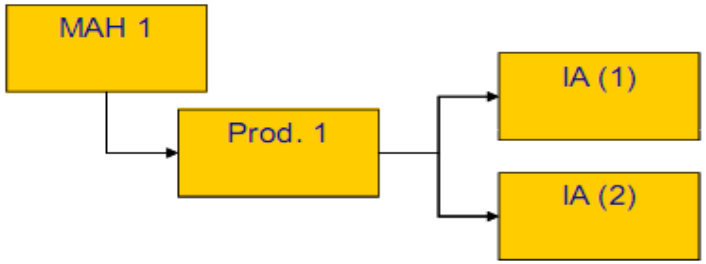
Type II: "Tell and wait"

Default for "unforseen"

New procedures

Grouping





Worksharing

….avoid duplication of work in the evaluation of variations to the terms of of several marketing authorisations….

Annex I
Extension- Changes to the active substance

1. Changes to the active substance(s):

(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:

(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;

Annex I
Extension- Changes to the active substance

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

Annex II
Classification of Variations

2. Major variations of type II shall comprise the following:

(a) Variations related to the addition of a new therapeutic indication or to the modification of an existing one

(b) Variations related to substantial modifications of the summary of product characteristics due to new clinical or pre-clinical findings;

(c) Variations related to changes outside the range of approved specifications, limits or acceptance criteria;

(d) Variations related to modifications in the manufacturing process of the active substance for a biological medicinal product;

(e) Variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines.

(g-k) veterinary medical product or vaccine human influenza

Classification Guideline-Structure
Impact of the Variation Regulation for Biologics

Presentation of variations according to MA dossier structure:

General introduction clarifying general principles e.g. *Ph.Eur.* updates

I. Administrative changes (no 1-7)

II. Quality changes (no 8-53)

1.	Active substance	*Manufacture, Control, Container closure system, Stability*
2.	Finished product	*Description/composition, Manufacture, Control of excipients, Control of finished product, Container closure system, Stability*
3.	CEP/TSE/monographs	
4.	PMF/VAMF	
5.	Medical devices	

III. Safety, Efficacy, Pharmacoviligance changes (no 54-69)

Appendix: **PMF/VAMF specific** changes (no 1-22)

Main concerns from Industry -1-

1. No “improvements” for biologicals/immunologicals

The active substance is not a biological / immunological substance.

The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods)

The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance

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

Biotechnological products are highly complex molecules

- **high molecular weight**

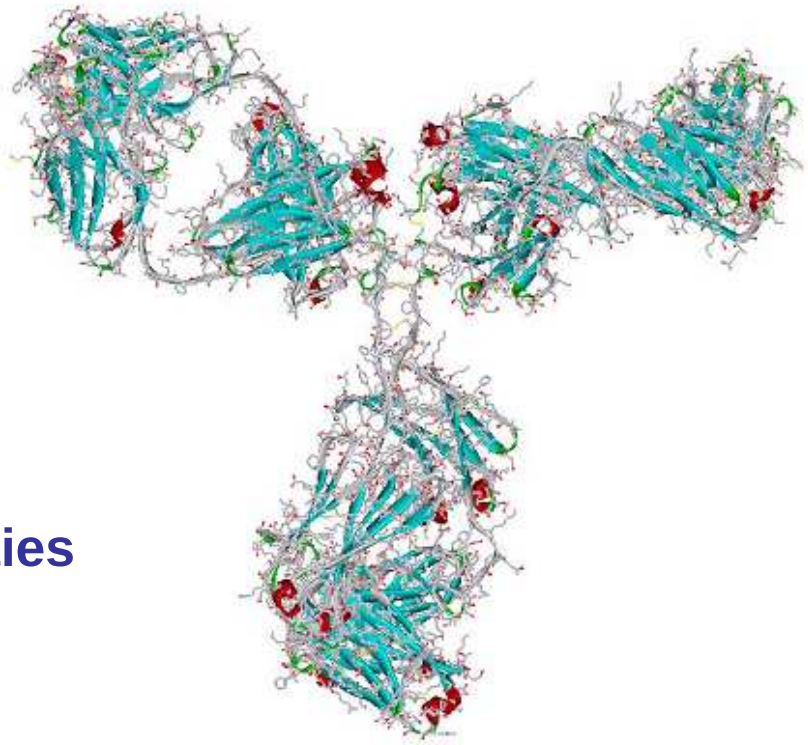
- **complexity**
  (primary / secondary / tertiary /
  quartery structure;
  post-translational modifications)

- **heterogeneity**

- **process- and product-related impurities**

- **species specificity**

- **immunogenicity**



Change to the active substance -type II-

B.I.a.2 Changes in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in the manufacturing process of the active substance	1, 2, 3, 4, 5, 6, 7	1, 2, 3	IA
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.		1, 2, 3, 4	IB

Conditions	
1.	No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties.
2.	The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.
3.	The specifications of the active substance or intermediates are unchanged.
4.	The change is fully described in the open ("applicant's") part of an Active Substance Master File, if applicable.
5.	The active substance is not a biological / immunological substance.
6.	The change does not refer to the geographical source, manufacturing route or production of a herbal medicinal product.
7.	The change does not refer to the restricted part of an Active Substance Master File.

IA condition not met

not listed as a Type II

'Default' Type IB?

Variation Regulation Annex II .2.

2. The following variations shall be classified as major variations of type II:

(e) variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product

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und biomedizinische Arzneimittel

DEFAULT ‘unclassified’ -1-

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Up to 10-fold increase compared to the currently approved batch size	1, 2, 3, 4, 6, 7, 8	1, 2, 5	IA
b) Downscaling	1, 2, 3, 4, 5	1, 2, 5	IA
c) The change requires assessment of the comparability of a biological/immunological active substance.			II
d) More than 10-fold increase compared to the currently approved batch size		1, 2, 3, 4	IB
e) The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line).		1, 2, 3, 4	IB
Conditions			
1. Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.			
2. Test results of at least two batches according to the specifications should be available for the proposed batch size.			
3. The product concerned is not a biological/immunological medicinal product.			
4. The change does not adversely affect the reproducibility of the process.			

→ ‘Default’ Type IB

Test method

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of in-process limits	1, 2, 3, 4	1, 2	IA
b) Addition of a new in-process test and limits	1, 2, 5, 6	1, 2, 3, 4, 6	IA
c) Deletion of a non-significant in-process test	1, 2	1, 2, 5	IA
d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance			II
e) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance			II
f) Addition or replacement of an in-process test as a result of a safety or quality issue		1, 2, 3, 4, 6	IB

→ ‘Default’ Type IB

?

6.	The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods)

Tightening of specification IA/IA$_{in}$

Addition of specification parameters IB

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits for medicinal products subject to Official Batch Release	1, 2, 3, 4	1, 2	IA$_{IN}$
b) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
c) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 7	IA

Type IB

Type IB

1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits

6.	The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeia

Include the new commercial specification galactosylation and sialylation testing Type IB

B.I.b) Control of active substance

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits for medicinal products subject to Official Batch Release	1, 2, 3, 4	1, 2	IA_{IN}
b) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
c) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 7	IA

Conditions
1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeia

DEFAULT 'unclassified'-2-

B.I.b) Control of active substance

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits for medicinal products subject to Official Batch Release	1, 2, 3, 4	1, 2	IA_{IN}
b) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
c) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 7	IA
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2	1, 2, 6	IA
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			II
f) Change outside the approved specifications limits range for the active substance			II
g) Widening of the approved specifications limits for starting materials/intermediates which may have a significant effect on the overall quality of the active substance and/or the finished product			II
h) Addition or replacement (excluding biological or immunological substance) of a specification parameter as a result of a safety or quality issue		1, 2, 3, 4, 5, 7	IB

Type IB

Rationale!

Change of test methods- Type II

Potency assays

identity (IEF, cIEF, CZE)

Purity

Impurities

B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	1, 2, 3, 4	1, 2	IA
b) Deletion of a test procedure for the active substance or a starting material/reagent/ intermediate, if an alternative test procedure is already authorised.	7	1	IA
c) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	1, 2, 3, 5, 6	1, 2	IA
d) Change (replacement) to a biological/ immunological/ immunochemical test method or a method using a biological reagent for a biological active substance. e.g. peptide map, glyco-map, etc.			II
e) Other changes to a test procedure (including		1, 2	IB

DEFAULT ‘unclassified’ -3-

B.I.c) Container closure system

B.I.c.1 Change in immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Qualitative and/or quantitative composition	1, 2, 3	1, 2, 3, 4, 6	IA
b) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances			II
c) Liquid active substances (non sterile)		1, 2, 3, 5, 6	IB

3	Sterile, liquid and biological/immunological active substances are excluded.

for frozen drug substance IB

Immediate Packaging –DS-

B.I.c.3 Change in test procedure for the immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	1, 2, 3,	1, 2	IA
b) Other changes to a test procedure (including replacement or addition)	1, 3, 4	1, 2	IA
c) Deletion of a test procedure if an alternative test procedure is already authorised	5	1	IA

Type IB

Conditions	
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
3.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
4.	The active substance/ finished product is not biological/immunological.
5.	There is still a test procedure registered for the specification parameter and this procedure has not been added through a IA/IA(IN) notification.

Immediate Packaging -DP-

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Non-sterile medicinal products	1, 2, 3	1, 2, 4	IA
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product			II IB
c) Sterile medicinal products		1, 2, 3, 4	IB

Stability

B.II.f) Stability

B.II.f.1 Change in the shelf-life or storage conditions of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Reduction of the shelf life of the finished product			
1. As packaged for sale	1	1, 2, 3	IA_{IN}
2. After first opening	1	1, 2, 3	IA_{IN}
3. After dilution or reconstitution	1	1, 2, 3	IA_{IN}

1	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

Extrapolation of stability data
Type II

b)	Extension of the shelf life of the finished product			
	1. As packaged for sale (supported by real time data)		1, 2, 3	IB
	2. After first opening (supported by real time data)		1, 2, 3	IB
	3. After dilution or reconstitution (supported by real time data)		1, 2, 3	IB
	4. Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH guidelines*			II
	5. Extension of storage period of a biological/ immunological medicinal product in accordance with an approved stability protocol.		1, 2, 3	IB
c)	Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol			II

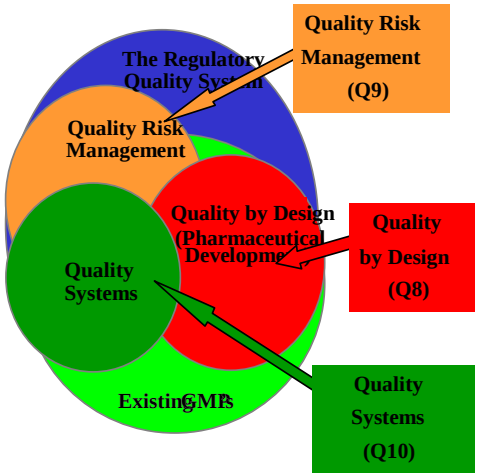
*Note: extrapolation not applicable for biological/immunological medicinal product

Main concerns from Industry-2-

2. Flexibility with regard to implementation of ICH Q8, Q9, Q10

B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures		1, 2, 3	II
b) Test procedures for starting materials/reagents/ intermediates and/or the active substance		1, 2, 3	II

Design space - (1)



Implementation of the ICH-concept

Design space:

- Annex II – Classification of Variations
- The following variations shall be classified as
- major variations of **Type II**:
  - Variation related to the introduction of a new design space or the extension of an approved one

Design space - (2)

- Design space:
  - proposed by the applicant
  - subject to regulatory assessment and approval.
  - it is the multidimensional combination and interaction of input variables and process parameters.

- Working within a design space
  - not considered as a change
  - movement out of the design space = change, which generates a Type II Variation

Ehrlich in seinem Arbeitszimmer