

December 2008

Proposals for the Guideline on Classification of Variations

Only those variations applicable to the active substance are listed.

A variation which is not an extension and whose classification is not laid down in this guideline shall be considered to be of Type IB.

A variation which is classified in this guideline as Type IA or Type IA_{IN} but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of Type IB.

A variation which is classified in this guideline as Type IB but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of Type II.

Title of Variation / Conditions to be Fulfilled		Type
3	Change in the name of the active substance	IA _{IN}
	Condition: The active substance shall remain the same.	
4	Change in the name and/or address of a manufacturer of the active substance where no Ph Eur Certificate of Suitability is available	IA _{IN}
	Condition: The manufacturing site shall remain the same.	
9	Deletion of any manufacturing site (including for an active substance where no Ph Eur Certificate of Suitability is available, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place)	IA
10 (i)	Minor change in the manufacturing process of an intermediate in the manufacture of the active substance	IA
	Conditions: <ol style="list-style-type: none"> 1. No negative impact on the impurity profile of any one of the following is demonstrated: <ul style="list-style-type: none"> – the intermediate immediately following the modified step – any suitable downstream intermediate – the active substance 2. The synthetic route remains the same, i.e. intermediates remain the same. 	

10 (ii)	Minor change in the final step of the manufacturing process of the active substance	IB		
	<p>Conditions:</p> <ol style="list-style-type: none"> No change in the qualitative and quantitative impurity profile or in physico-chemical properties of the active substance, i.e. <ul style="list-style-type: none"> specified impurities remain within their approved limits no new impurities above the identification threshold are detected residual solvents remain within ICH limits The synthetic route remains the same, i.e. intermediates remain the same. 			
11	Change in batch size of active substance or intermediate	IA		
	<p>Conditions:</p> <ol style="list-style-type: none"> Any changes to the manufacturing methods are only those necessitated by scale-up, e.g. use of different sized equipment. Test results of at least two batches according to the specifications should be available for the proposed batch size. The change does not affect the reproducibility of the process. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 			
12 (i)	Change in the specification of an active substance	IA IA		
	<table border="0"> <tr> <td>a) Tightening of specification limits</td> <td>Condition 1</td> </tr> <tr> <td>b) Addition of a new test parameter</td> <td>Condition 2</td> </tr> </table> <p>Conditions:</p> <ol style="list-style-type: none"> Any change should be within the range of currently approved limits. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 		a) Tightening of specification limits	Condition 1
a) Tightening of specification limits	Condition 1			
b) Addition of a new test parameter	Condition 2			
12 (ii)	Change in the specification of a starting material / intermediate / reagent used in the manufacturing process of the active substance	IA		
	Condition: No change to the specifications of the active substance.			
13 (i)	Change in test procedure for an active substance	IA IB		
	<table border="0"> <tr> <td>a) Minor change to an approved test procedure</td> <td>Conditions 1, 2, 3</td> </tr> <tr> <td>b) Other changes to a test procedure, including replacement or addition of a test procedure</td> <td>Conditions 2, 3</td> </tr> </table> <p>Conditions:</p> <ol style="list-style-type: none"> 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); no new impurities are detected above the identification threshold. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines. Results of method validation show new test procedure to be at least equivalent to the former procedure. 		a) Minor change to an approved test procedure	Conditions 1, 2, 3
a) Minor change to an approved test procedure	Conditions 1, 2, 3			
b) Other changes to a test procedure, including replacement or addition of a test procedure	Conditions 2, 3			

13 (ii)	Change in test procedure for a starting material, intermediate or reagent used in the manufacturing process of the active substance	IA
	Condition: New test procedure to be at least equivalent to the former procedure.	
14 (i)	Change in the manufacturer of the active substance where no Ph Eur Certificate of Suitability is available	IA IB
	<p>a) Change in site of an already approved manufacturer (replacement or addition) Conditions 1, 2, 3</p> <p>b) New manufacturer (replacement or addition) Conditions 1, 2, 3</p> <p>Conditions:</p> <p>1. The specifications (including in-process controls, methods of analysis of all materials), method of preparation and detailed route of synthesis are identical to those already approved or any further modifications fall under Type IA or IB variations.</p> <p>2. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current <i>Note for Guidance on Minimising Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products</i>.</p> <p>3. The change does not concern a biological medicinal product.</p>	
14 (ii)	Change in manufacturer of a starting material, intermediate or reagent used in the manufacturing process of the active substance where no Ph Eur Certificate of Suitability is available	IA
	Conditions: No change to the specifications of the active substance.	
15	Submission of a new or updated Ph Eur Certificate of Suitability for an active substance or starting material / reagent / intermediate in the manufacturing process of the active substance	IA IB IA _{IN} IB IA IB
	<p>a) From a manufacturer currently approved Conditions 1, 2a, 2b, 4 Conditions 1, 2a, 4</p> <p>b) From a new manufacturer (replacement or addition) Conditions 1, 2a, 2b, 3, 4 Conditions 1, 2a, 3, 4</p> <p>c) Substance in veterinary medicinal product for use in animal species susceptible to TSE Conditions 1, 2a, 2b, 3, 4 Conditions 1, 2a, 3, 4</p> <p>Conditions:</p> <p>1. The finished product release and end of shelf life specifications remain the same.</p> <p>2a. Unchanged additional (to Ph Eur) specifications for product specific requirements (e.g. particle size profiles, polymorphic form) if applicable.</p> <p>2b. Unchanged additional (to Ph Eur) specifications for impurities if applicable, excluding residual solvents when the only change is in compliance with ICH Q3C (in which case Type IA applies). Note – this condition is only intended to apply to situations in which specification limits for new impurities are added.</p>	

	<p>3. The active substance will be tested immediately prior to use if no retest period is included in the Ph Eur Certificate of Suitability or if data to support a retest period is not provided.</p> <p>4. The manufacturing process of the active substance, starting material / reagent / intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.</p>	
16	Submission of a new or updated TSE Ph Eur Certificate of Suitability for an active substance or starting material / reagent / intermediate in the manufacturing process of the active substance for a currently approved manufacturer and currently approved manufacturing process	IA
17	<p>Change in:</p> <p>a) Retest period of the active substance</p> <p>b) Storage conditions for the active substance</p> <p>where no Ph Eur Certificate of Suitability stating the retest period is available.</p> <p>Conditions:</p> <p>1. Stability studies have been done according to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.</p> <p>2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.</p>	IA
25	<p>Change to comply with Ph Eur or with the national pharmacopoeia of a Member State</p> <p>a) Change of specification(s) of a former non-European pharmacopoeial substance to comply with Ph Eur or with the national pharmacopoeia of a Member State</p> <p>b) Change to comply with an update of the relevant monograph of the Ph Eur or national pharmacopoeia of a Member State</p> <p>Conditions:</p> <p>1. The change is made exclusively to comply with the pharmacopoeia.</p> <p>2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form) if applicable.</p>	IA
NEW	Change in the packaging of the active substance	IA
NEW	<p>Redefinition of an intermediate as a starting material in the synthesis of the active substance</p> <p>Conditions:</p> <p>1. The new starting material is adequately controlled.</p> <p>2. No change to the specifications of the active substance.</p>	IB

NEW	Change in the manufacturer of the active substance where no Ph Eur Certificate of Suitability is available, which leads to a change in the specifications of the active substance, which is not classified as a Type IA or IB variation.	II
NEW	Change in the manufacturing process of the active substance involving a change to the route of synthesis or which leads to a change in the specifications of the active substance, which is not classified as a Type IA or IB variation.	II