# Comments to proposal for revised classification guideline

**BI.a.1 Change in the manufacturer of a starting material/reagent/intermediate…**

B.I.a.1.c - It is not clear when this category is to be chosen by an applicant and we have never seen a variation application where this category has been chosen. In the proposed guideline, there are now two "straight forward" options for new manufacturers using a non-approved manufacturing process, category b when supported by an ASMF and category g when not supported by an ASMF. The need for c could therefore be reconsidered or it could be clarified when this category is to be chosen.

**B.I.a.2 Changes in the manufacturing process of the active substance**

A relatively common proposed change is the removal of process parameters from the description of the manufacturing process, *e.g.* criteria for temperature, pH etc and amounts of solvents and reagents. In many cases where this is proposed, an introduction of a design space would be a much more appropriate approach. In other words, instead of introducing an operational range for the criteria of the process parameters as would be most appropriate, the parameters are simply proposed to be removed from the description allowing full flexibility. This is sometimes applied for as category B.I.a.2.a (minor change, type IA) with the justification that the change does not impact the actual manufacturing process, only the description of the process (all conditions are still fulfilled since the synthetic route remains the same). In some cases this is applied for as B.I.a.2.z (typically type IB) since there is not suitable category for this kind of change. It is proposed that a new category is introduced that takes these kind of proposed changes into account: "Change to the level of details in the manufacturing process description". As an option to this, the condition 2 is proposed to be expanded with a sentence "There are no significant changes to any process parameters".

Routine reprocessing is very often applied for as type IA in category B.I.a.2.a. With the current guideline, this is considered a valid notification since all conditions are fulfilled. Routine reprocessing should preferable be applied for as a type IB since any need for routine reprocessing should be justified. It is therefore proposed to introduce a new condition or expand an already existing condition for category B.I.a.2.a with "No new reprocessing procedure is introduced."

**B.I.d.1 Change in the re-test period…**

The documentation requirement 2 states "Confirmation that stability studies have been done to the currently approved protocol." The protocol has typically not yet been approved by any national authority or the EDQM when applying for an introduction of a retest period (a.4). The documentation requirement is therefore proposed to be revised to take this into account.

**B.II.b.3 Change in the manufacturing process of the finished product**

Removal of already approved criteria for process parameters are often applied for as type IA using the category B.II.b.3.a. Although most of these applications concern removal of criteria for non critical process parameters, it is proposed that a new category is introduced that takes these kind of changes into account: "Change to the level of details in the manufacturing process description". As an option to this, the condition 2 is proposed to be expanded with a sentence "There are no significant changes to any process parameters". (Also refer to the comment above regarding the same issues for active substance)

**B.II.b.4 Change in the batch size (including batch size ranges) of the finished product**

B.II.b.4.a – For products containing drug in low content (≤2% of composition)* we would normally expect process validation data to be submitted for a change in batch size up to 10-fold, not only see a protocol. Hence, a type IB variation rather than a Type IA notification would better apply for these specialized pharmaceutical dosage forms. This could be solved by amending condition 2 to clearly exclude drug products containing ≤2% of active substance in the composition.

*Reference is made to Note for Guidance on Process Validation (CPMP/QWP/2054/03, EMEA/CVMP/395/03).

**B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability…**

B.III.1.a.5 - The sentence (in case multiple certificates exist per material) is proposed to be removed. In some cases this is not a valid condition, for example when one API manufacturer has an ASMF and another API manufacturer has a CEP. This issue should already be sufficiently covered by the condition 10.

B.III.1.a.3 (replacement) and B.III.1.a.5 – It is proposed to add the condition: "The deletion or replacement should not be due to critical deficiencies concerning manufacturing" (in analogy with this condition for variation category A.7). The rationale for the proposal is to prevent IA notifications to delete or replace a site where the CEP has been suspended/withdrawn due to GMP issues.

**B.III.2 Change to comply with Ph. Eur…**

Removal of tests for relevant in-house impurities and in-house analytical methods for these are sometimes applied for as type IA using category B.III.2. Condition 1 is proposed to be expanded with the sentence "The specifications for relevant in-house impurities and analytical methods for these remains the same."