Q/A-LIST FOR THE SUBMISSION OF VARIATIONS ACCORDING TO COMMISSION REGULATION (EC) 1084/2003

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Question 1.
When and how should the variation be submitted to RMS and CMS?

Answer: According to the Regulation (EC) 1084/2003 the same application and the same documentation should be submitted simultaneously to the RMS and all CMS.

Question 2.
Which Type of variation should be submitted when the particular change we are applying for is not mentioned in Annex I of the Regulation, or one or more of the conditions cannot be fulfilled?

Answer: If a change is not mentioned in Annex I or the conditions for a specific change could not be fulfilled, this change has to be submitted as a Type II variation.

Question 3. *Which documents have to be submitted for a variation Type IA, IB or II before a procedure is started?*

Answer: The application form incl. all relevant documentation (e.g. SmPCs, labels and leaflets as required and also national information texts, checklist etc.) has to be submitted to the RMS and all CMS. The procedures will not be started before the RMS has received the dispatch list with the dispatch date for all CMS including a statement of the applicant that the fees have been paid, where applicable.

Question 4. *What is exactly meant with # 7c ("all other manufacturing operations except batch release"?*

Answer: This should be interpreted as all manufacturing operations excluding primary packaging, secondary packaging and batch release. It should not be read as all manufacturing operations excluding batch release.

Question 5. *Primary packaging of a sterile product is excluded from variation #7(b). We wish to change the manufacturer of a sterile finished product, can this be submitted under #7(c)?*

Answer: Changes in manufacturing sites for sterile products, that involve primary packaging, are Type II variations. Change 7(c) is for 'all other manufacturing operations' excluding primary and secondary packaging and batch release. As the filling of sterile products is excluded from change 7(b) it is also excluded from change 7(c). However, certain unit operations used during the manufacture of sterile products that do not involve the primary packaging e.g. sterilisation post filling and sealing may be submitted as a #7(c).

Question 6. *How to apply for the deletion of more than one manufacturing site*?

Answer: In case more than one manufacturer has to be deleted separate parallel type IA notifications for each manufacturing site have to be submitted.

Question 7. *How to apply for a change in the manufacturer of an active substance or starting material/reagent/intermediate?*

Answer: If a DMF is used, then a new DMF has to be submitted and therefore the MAH should apply for a Type II variation. The applicant has normally no access to the closed part of the DMF and therefore is not in the position to state that there are no changes in the specifications, route of synthesis and method of preparation (see also question # 18). In cases where no DMF or Certificate of Suitability is used (and the applicant has included all the documentation regarding the a.s. in the registration dossier), variation No. 14b can be used.
In cases where a CoS is used, the MAH should apply for a variation No. 15a.

Question 8. *We wish to submit a new CEP for an active ingredient (#15) but the CEP does not state a retest period and we have stability data to support a retest period. Can we tick condition 3 and include the stability with the Type IA #15?*

Answer: The stability data will need to be assessed and therefore a parallel variation #17 concerning the retest-period has to be submitted and this has to be stated by the applicant in the application form and checklist of the #15 application. As the #17is a Type IB change, condition 3 of #15 will have to be ticked as omission of re-testing will not be acceptable until the #17 change is approved.

Question 9. What should we do if there is an update of a pharmacopoeial monograph?

Answer: If the change in the general monograph or monograph for active substance or excipient is implemented within 6 months after publication and when reference is made to the "current edition" in the dossier, there is no need to submit a variation (see introductory text of Annex I).
When the update of the general monograph affects the finished product specifications and the change is implemented later than 6 months after publication or a specific version of the monograph is mentioned in the dossier a variation #37 or #38 has to be submitted. When the update of a monograph for active substance or excipient is implemented later than 6 months after publication, or a specific version of the monograph is mentioned in the dossier, a variation # 25 has to be submitted.Note: There is a legal requirement of the MAH to comply with an update of the Pharmacopoeia within the legal foreseen timeframe.

Question 10. *When applying for a change in the supplier of packaging components (variation #30) what should be done if condition #2 is not met because there is a change in the quantitative or qualitative packaging material?*

Answer: In this particular example the main change is actually the packaging material and not the change in supplier. Consequently, a single variation #29 (Change in the composition of packaging material) should be submitted with the change in supplier (#30) being consequential.

Question 11. *One of the conditions (condition #2) for variation #32, for a change in the batch size of the finished product is that the pharmaceutical form is a standard immediate release oral form or non-sterile liquid form. What should we do if we want to increase the batch size of an ointment, suppository or other pharmaceutical form?*

Answer: As all other pharmaceutical forms (e.g. plasters, ointments, suppositories etc.) are excluded by condition #2 a Type II variation has to be submitted.

Question 12. *When may a "minor" change in the manufacturing process according to variation #33 be submitted and what documentation is required to support the change ?*

Answer: By definition a 'minor change' is a Type I notification. Therefore the conditions as listed in Annex I of Regulation 1084/2003 have to be fulfilled and sustained by the relevant documents. The amended section of Part IIB or the equivalent in the CTD format required as documentation #1 should include a direct comparison of the present process and the new process (by analogy with variation #10). In this case the old and the new flow-chart for the manufacturing process should be presented side by side.

Question 13. *Will variation #12b or #37b apply, if a new impurity has to be added to the specification of the active ingredient or finished product?*

Answer: New impurities which are detected with new test parameters and which are outside the approved limits or new impurities detected with old test parameters are regarded as an unexpected event during the manufacture. Therefore, this change is excluded as a notification by condition #2. The change has to be applied for as Type II variation. If the impurity was previously in the product but not detected (due to specificity of the method) and there is no change to the total impurity limits in the specification, this can be processed as a Type IB variation.

Question 14. *Which documentation has to be added to the application if a change in pack size is applied for e.g. only changing the number of blisters in a pack without changing the nature of the blister? Is the submission of documentation #1 (amendment to part II) and #3 (declaration about stability studies) necessary?*

Answer: For a change in pack size (variation #41a) documentation #1 and #3 has to be submitted. However, if there is only a change in the number of the blisters, but no change to the nature of the blister itself the documentation may be omitted and the MAH must provide a justification. If no stability parameters are affected by the change this should be stated in the declaration.

Question 15. *What type of application is required for a deletion of pack sizes*?

Answer: A Type IA notification #41a may be submitted if the currently approved pack size range does not change. If the pack size to be deleted is the smallest or largest pack size in the currently approved range, a notification IB has to be submitted (#41a2).

Question 16. *How to apply for minor changes in the restricted part of the DMF/ASMF?*

Answer: As the applicant normally has no access to the restricted part of the DMF and therefore cannot declare that the relevant conditions are met or cannot provide all relevant documents, these changes will usually have to be applied for as type II variations. However, if the relevant conditions can be fully addressed, Type IB variations may be submitted.

Question 17. *How will a change in the dimension of a transdermal patch without changing the area of the patch be processed*?

Answer: As variation #40 only applies for tablets, capsules, suppositories or pessaries there is no possibility to apply for a change in the dimension of other pharmaceutical forms via a Type IA/IB notification. A Type II variation has to be submitted.

Question 18. *How to apply for a new manufacturing site of the finished product where e.g. there is an alternative batch size or minor changes in the manufacturing process (alternatively to the approved manufacturing process in other manufacturing sites)?*

Answer: These variations should be submitted as parallel variations and not as consequential variations.

Question 19. *Which Type of variation has to be submitted when there is a change in the active substance manufacturer (variation #14) but condition #1 is not met, as there are changes in the batch size or manufacturing process?*

Answer: A Type II variation has to be submitted because condition #1 is not met.

Question 20. *If a new or updated CEP is submitted or a DMF is replaced by a CEP (variation #15) what should be done if conditions #1 and/or #2(specifications are unchanged and product specific impurities are unchanged) are not met?*

Answer: A Type II variation has to be submitted because condition number 1 and/or number 2 are not met. In the event that the only change regarding the specification for impurities is a change in the residual solvents that is in compliance with the ICH-limits (Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95)) and where the relevant Option 1 limit is applied to Class 2 solvents, no Type II variation is necessary and the change may be submitted according to Annex I.

Question 21. *Can the same variation for more than one product be submitted on one application form?*

Answer: No, one application form has to be submitted for each pharmaceutical form and strength. However, if the supportive documentation for different strengths and/or pharmaceutical forms is the same this may be added once to the application. For the required number of copies of the application forms and supportive documentation reference is made to Chapter 7 of the NtA, volume 2A.

Question 22. *Is it necessary to submit variation applications to all concerned member states even if they are not concerned by the specific change (e.g. change in the address of the MAH in only one CMS)?*

Answer: Yes, the applications have to be submitted to all Concerned member states.

Question 23. *A change in the primary packaging material for the active substance is not defined as a Type IA or IB variation. How should these changes be submitted?*

Answer: The primary packaging of the active substance is regarded as part of the manufacture of the active substance. Therefore, a change in the primary packaging material may be submitted as a Type IB variation under #10 Minor change in the manufacturing process of the active substance.