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Human Medicines Division Pre-notification check for Type IB Variations

This pre-notification checklist is aimed at facilitating submission of complete and correct Type IB variation notifications by marketing authorisation holders (MAHs).

Guidance for marketing authorisation holders

The Agency strongly recommends that this checklist is used in advance of submission of any Type IB variation; you should be able to answer "Yes" to every item listed below unless a specific point is not applicable ("n/a") to the application in question. Please note that this checklist should not be included in the submission.

Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') defines a minor variation of Type IB as a variation that is neither a Type IA variation nor a Type II variation nor an extension. Such minor variations must be notified to the national competent authority or the European Medicines Agency (the Agency) by the MAH before implementation, but do not require a formal approval. Upon acknowledgement of receipt of a valid notification, the MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the national competent authority or the Agency before implementing the change ('tell, wait and do' procedure).

Upon receipt of a Type IB application, the procedure manager proceeds to validate the documentation submitted in accordance with the checklist included below. The validation issues included in the checklist are presented below in different fonts (**bold**, *italics* and normal) to facilitate understanding on the points that would prevent the start of the procedure until they are addressed satisfactorily from those that facilitate validation or assessment:

- **Bold** corresponds to blocking validation issues that need to be satisfactorily addressed by the MAH before the start of the procedure;
- *Italics* corresponds to validation issues that relate to information needed for documentation check but not blocking;
- Normal corresponds to information considered for completeness of the submission and not blocking. These issues can be either raised at validation together with other **Bold** or *italic* validation issues or, if no bold or italic validation issues are identified, they are highlighted in the variation report for improvement of future submissions.

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Issues identified during validation will be notified to the MAH via email. The MAH will be requested to provide responses to the issues raised within 5 working days. Delayed or insufficient responses will lead to complete or partial invalidation (in case of grouped variations) of the application as only one request for supplementary information will be issued during the validation phase.

For variations affecting an Active Substance Master File (ASMF), an additional section of the checklist is presented addressing the specific submission requirements.

Type IB Pre-notification checklist

Type IB submission checklist[1]	Yes	n/a
TECHNICAL SUBMISSION REQUIREMENTS		
• Dossier is submitted in eCTD format[2] and is technically valid (i.e. has passed eCTD technical validation criteria).		
COVER LETTER		
• Present, dated and signed. • Refers to the same medicinal product(s), EU number(s) and procedure as listed in the Application Form. • Where applicable, previous regulatory and/or procedural advice requested to the Agency is attached. • For worksharings, include a short overview of the nature of the changes and, if a group is included in the worksharing, indicate whether it is submitted under Article 7.2(b) or (c) of Variations Regulation.		
APPLICATION FORM[3]		
• **Present, correct version, dated.** • **Variation procedure number(s) should be left blank,** except in case of a worksharing procedures where the procedure number needs to be obtained in advance via EMA service desk. • **The name and address of the MAH and of the contact person are stated** with the organisation details **filled from SPOR OMS.**		
'Type of application' • Correctly identified by ticking the box(es) Type IA, Type IA$_{IN}$ (in case of grouped variations) and Type IB or Type IB unforeseen. • Indicates all types of changes present in the submission. • Indicates whether it is a single or a grouped submission. • Indicates whether it is a worksharing.		
'Products concerned by this application' • EU marketing authorisation number(s) and National marketing authorisation number(s), as applicable for worksharing, of (all) affected presentation(s) is/are listed.[4] • Is/are the same as that/those indicated in the Present/Proposed table, Precise Scope and cover letter.		
'Types of change(s)' • **All changes applied for are correctly classified according to the Guideline on the details of the various categories of variations** or a recommendation on an unforeseen variation according to Article 5 of Commission Regulation (EC) No 1234/2008**.**		

[1] Guidance for submitting Type IB variations is provided in the post-authorisation guidance "Q&A: Type IB variations".
[2] Please refer to the "eSubmission: eCTD".
[3] Please refer for guidance to "PLM Portal" and "eSubmission".
[4] Please avoid stating 'See Annex A' if **not** all presentations are affected by the change(s) applied for.

Type IB submission checklist[1]	Yes	n/a
• **When two or more changes fall under the same indent, the variation classification category is indicated as many times as there are changes (e.g. scope Q.II.e.6.a.2 is repeated 'x' times for 'x' additional new pack sizes).** • **In case of grouped variations including changes categorised as Type IA,** **- the date of implementation for Type IA changes is provided.** **-** the Type IA variation has been submitted within 1 year (Type IA) or immediately following implementation (Type IAIN), as appropriate. **-** For worksharing applications, the same scope(s)/(change(s)) must be applied to all products concerned by the application. The scope(s) applied for **should not** be repeated for each product. • **Relevant conditions and documentation, as specified in the Guideline on the details of the various categories of variations** or a recommendation on an unforeseen variation according to Article 5 of Commission Regulation (EC) No 1234/2008 **are ticked.**		
'Precise scope and background for change' It contains for each change applied for in the section 'Types of Change(s)': • A variation classification category and a precise description of the change[5]. If the Product Information (PI) is affected, the sections updated should also be provided here. • When two or more different changes fall under the same scope, the variation classification category is indicated as many times as there are changes (e.g. scope Q.II.e.6.a.2 is indicated for each additional new pack size). • Additional background information should be included as applicable as a separate paragraph.		
'Present and Proposed' table (or provided as an attachment) • *Reflects all the changes applied for in the section 'Types of Change(s)' including editorial changes.* • For clarity, the present and proposed wording is, for each scope, presented under the relevant variation classification category. • Shows the precise present and proposed wording as in the relevant sections of the dossier and, if applicable, in the PI. For further guidance, see footnotes 9 and 10[6] of the Application Form (identifies the changes with the appropriate highlights). • Dossier section number(s) is/are indicated at the lowest possible level. • *When changes result in any updates of manufacturing sites (i.e. name/address change, addition or replacement of manufacturing site(s) or the Marketing Authorisation Holder) the present/proposed table is completed by selecting the organisation from SPOR/OMS to autofill address details.* • All editorial changes are included and a justification as to why they are considered editorial is included in the application.		
'Annexed documents (where appropriate)' • Relevant boxes are selected or left un-ticked as appropriate. If changes to the Annex II of the PI are proposed, the box "Manufacturing Authorisation Holder responsible for batch release and conditions of the Marketing Authorisation" should be ticked.		
'Declaration of the Applicant' Boxes relating to the aspects below are ticked: • **"There are no other changes than those identified in this application [...]".** • "Where applicable, all conditions as set for the variation(s) concerned are fulfilled". • "For Type IA notifications: the required documents as specified for the changes concerned have been submitted" (if included as part of the grouped variations).		

[5] Please refer to the "Guidance for applicants for the preparation of the 'precise scope' section of the variation application form".
[6] As stated in the eAF "For SPC, labelling and package leaflet (PL) changes, underline or highlight the changed words presented in the table above or provide as a separate Annex".

Type IB submission checklist[1]	Yes	n/a
• **In case of a worksharing involving medicinal products approved within the mutual recognition procedure or nationally, this application has been submitted simultaneously to the relevant National Competent Authorities and the EMA. The box "For mandatory worksharing or (super-)grouped variations affecting more than one MA: The MAs concerned belong to the same MAH" is ticked, as relevant.** • **Date of implementation of the Type IB changes is inserted.** • **The box "The applicant confirms that the same variation (or group of variations) does not apply to any other marketing authorisation held by the same holder" is ticked.**		
Grouping is acceptable, either as outlined in Annex III of the Variations Regulation or previously agreed with the Agency.		
SUPPORTING DOCUMENTATION		
Relevant documentation listed in Annex IV of the Variations Regulation and in the Commission Classification guideline is provided. • *Included and presented in accordance with the appropriate EU-CTD format headings and numbering.* • *Is complete, updated, and correctly reflects the changes listed in the Present and Proposed table.* • *Affected section(s) of the dossier correctly show the change(s) applied for.*		
PRODUCT INFORMATION (SMPC (ANNEX I), ANNEX II, LABELLING (ANNEX IIIA), PL (ANNEX IIIB)) AND ANNEX A		
• The PI includes only changes declared in the Present and Proposed table in the Application Form. • **The PI is provided in all EEA languages in Word format (with tracked changes in anonymised format, including the required statement[7]) and as clean PDFs correctly formatted[8] and named (according to the formatting checklist[9]). No other versions or formats are included.** • **The PI correctly reflects the scope of the variation and is based on the latest approved version.** • **Annex A[10] is provided in all EEA languages in Word format (with tracked changes) and as clean PDFs when its content is modified by a change (e.g. addition or deletion of a presentation).** • **The formatting checklist for minor procedures without linguistic review[9] has been completed and included in the submission.**		
New EU number(s) • Reserved with the EMA[11]. • Correctly inserted in Annex A, in the Product Information.		
CHANGES TO THE RMP		
• **The Version number is correctly reflected.**		

[7] Please refer to the "Statement to be included in the tracked changed product information annexes when submitting the final translations to the Agency".
[8] Please refer to the "User guide on how to generate PDF versions of the Product Information and other annexes - human".
[9] Checklist for the submission of product information annexes and Annex A (if applicable) for minor procedures without linguistic review.
[10] Please see the "Annexe A QRD Template".
[11] New EU sub-numbers for Type IB variations concerning an additional presentation (e.g. new pack size) should be requested to the European Medicines Agency prior to the submission of the procedure. Please refer to Q.11 of the published post-authorisation guidance 'Q&A: Type IB variations'.

Type IB submission checklist[1]	Yes	n/a
• The changes to the RMP should be included in the Application Form in the 'Present and Proposed' table or provided as a separate Annex (except in case of update to the latest RMP template). • **RMP, based on the latest approved version, only including the changes covered by the scope of the variation with tracked changes, or** • **RMP including a summary of changes from the previous RMP version (mandatory in case update to the latest RMP template).** • **The redacted RMP (clean and tracked) and the signed RMP Publication Declaration[12], ensuring personal data and commercial confidential information[13] are removed, is provided.**		
CHANGES TO AN ASMF		
MAH should submit: • **Application Form listing the ASMF number {EMEA/ASMF/xxxxx or EU/ASMF/xxxxx} in the 'Present and Proposed' table (last row).** In order to avoid validation comments, the EMA strongly recommends the submission of the variation application once the ASMF holder has requested and obtained an EMEA ASMF reference number[14] and has successfully carried out the submission of relevant sections of the ASMF in the appropriate eCTD format. • **Revised sections of the dossier (Applicant's Part) corresponding to ASMF Holder's Applicant's part.**		
MAH should liaise with ASMF holder to ensure that the following documentation is submitted: • Submission letter and administrative details (Annex 3 of the ASMF Guideline)[15,16]. • Detailed table of changes, clearly showing the present and proposed situation. Dossier section number(s) is/are indicated at the lowest possible level. • **Revised sections of the ASMF dossier (Applicant's/Restricted Part) reflecting changes to the previously accepted version, as applicable.**		
IMPLEMENTATION OF AN OUTCOME - C.3 SCOPE		
• Application Form listing reference to the recommendation of the competent authorities. • The agreed wording is correctly reflected in all applicable sections of the SmPC and PL as published on the EMA website. • Annexes provided in Word format (with tracked changes) and as clean PDF correctly formatted[9]. No other versions or formats are included.		
CHANGES IN THE CLINICAL USE OF A PRODUCT, MEANING CHANGE IN THERAPEUTIC INDICATION, POSOLOGY OR MAXIMUM DAILY DOSE[17]		
If a quality variation is not required: • Declaration in the Application Form or as a separate Annex in Module 1 confirming the conclusions of assessment of the impact on the quality documentation of the proposed clinical change.		

[12] Please refer to question 16.14 of "EMA's post-authorisation procedural advice for users of the centralised procedure".
[13] Please refer to the "Guidance on the anonymisation of protected personal data and assessment of commercially confidential information during the preparation and redaction of risk management plans".
[14] Please refer to Q.3.3.6 of the Pre-authorisation guidance"How shall I submit an Active Substance Master File (ASMF)? ".
[15] Please refer to the "Guideline on Active Substance Master File Procedure".
[16] Please refer to the "Additional guidance on documents relating to an active substance master file".
[17] Please refer to question 7.3.1 of "EMA's post-authorisation procedural advice for users of the centralised procedure".

Type IB submission checklist[1]	Yes	n/a
CHANGES IN THE PRODUCT INFORMATION FOR A GENERIC/HYBRID/BIOSIMILAR ALIGNING WITH THE REFERENCE PRODUCT		
MAH should: • Include a detailed precise scope for the changes implemented, including relevant PI sections affected. • Include a copy of the relevant English track changes PI(s) of the reference medicinal product. • Include a confirmation in the eAF that the translations have been implemented in line with the translations of the reference medicinal product. • For changes in the PI of a biosimilar aligning with an indication of the reference product: provide a justification that the comparability exercise performed for the biosimilar medicinal product is valid for the applied indication.		

This checklist is published for transparency purposes and does not preclude that during the actual validation of the submitted application the Agency may identify other issues that could impact the validation outcome.