Bundesinstitut
für Arzneimittel
und Medizinprodukte

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Pre-notification check for type IB Variations [1]

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 BfArM strongly recommends that this checklist is used in advance of submission of any Type IB variation; you should be able to answer to every item listed below "Yes" 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 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 before implementing the change ('tell, wait and do' procedure). For changes of variation category A.2b, an official notification will be issued by BfArM in accordance with § 29(2) German Drug Law.

Upon receipt of a type IB application, the validation unit 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** 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;
- 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 validation issues or, if no bold validation issues are identified, they may be notified for improvement of future submissions.

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 10 working days. Delayed or insufficient responses may lead to complete or partial invalidation (in case of grouped variations) of the application as only one request for supplementary information should usually be issued during the validation phase.

For variations affecting an Active Substance Master File (ASMF), changes to the Risk Management Plan (RMP) or implementation of a PRAC signal recommendation wording additional sections of the checklist are presented addressing the specific submission requirements.

Type IB Pre-notification checklist

Type IB submission checklist[2]	Yes	n/a
TECHNICAL SUBMISSION REQUIREMENTS		
• Dossier is submitted in eCTD[3] and is technically valid (i.e. has passed eCTD technical validation criteria).		
COVER LETTER[4]		
• Present, dated and signed. • Refers to the same medicinal product(s), MA- and, if applicable, MR/DC-numbers and variation procedure number as listed in the application form. • Where applicable, previous regulatory and/or procedural advice requested to the competent authority is attached.		
APPLICATION FORM[5]		
• **Present, correct and current version, dated and signed by the MAH or a letter of authorisation is attached.** • **Correct variation procedure number according to CMDh Best Practice guide for variations, chapter 1 or – for purely national variations - BfArM 2nd announcement dated 15 July 2016 respectively[10].** • **Complete and correct listing of the concerned member state(s). If no CMS is affected have to be "none" ticked.** • **States the name and address of the MAH and of the contact person (with email-address).**		
'Type of application' • Correctly identified by ticking the box(es) Type IA, Type IA$_{IN}$ (in case of grouped variations) and Type IB. It should also be specified whether the procedure is foreseen or unforeseen in the classification guidance. • **Indicates whether it is a single or a grouped submission.**		
'Products concerned by this application' • **States the correct and complete invented name with strength and pharmaceutical form to the RMS and all CMS. Marketing authorisation number(s) and, if applicable, MR/DC- numbers of (all) affected presentation(s) is/are listed.**[6] • Is/are the same as that/those indicated in the Present/Proposed table, Precise Scope and cover letter.		

Type IB submission checklist[2]	Yes	n/a
'Types of change(s)' • **All changes applied for are correctly classified according to the Guideline on the details of the various categories of variations (2013/C 223/01).** • **When two or more changes fall under the same category, the scope number is indicated as many times as there are changes (e.g. scope B.II.e.5.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 IA$_{IN}$), as appropriate** • **In case of variation(s) affecting more than 1 Marketing Authorisation:** – **the same (group of) variation(s) is applied for all Marketing Authorisations** • **In case of inclusion of editorial changes:** – **CMDh Q/A on variations no. 3.16 and the EMA Post-authorisation Guidance Q&A on Editorial Changes (for Module 3 changes) is considered, resp.**		
'Precise scope and background for change' It contains for each change applied for in the section 'Types of Change(s)': • A scope number and **a precise description of the change**. 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 scope number is indicated as many times as there are changes** (e.g. scope B.II.e.5.a.2 is indicated for each additional new pack size). • For unforeseen variations, a justification for the classification should be included. • A justification for the grouping should be included, if applicable. • When a IA$_{IN}$-Variation is not submitted immediately, a justification for the delay should be included.		
'Present and Proposed' table • **Reflects all the changes applied for in the section 'Types of Change(s)'.** • Shows the precise present and proposed wording as in the relevant sections of the dossier and, if applicable, in the Product Information. For further guidance, see footnotes 9 and 10 of the application form. • Dossier section number(s) is/are indicated at the lowest possible level.		
'Annexed documents (where appropriate)' • Relevant boxes are selected or left unticked as appropriate.		

Type IB submission checklist[2]	Yes	n/a
'Declaration of the Applicant' The 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). **In case of a worksharing involving medicinal products approved within the mutual recognition procedure and/or nationally, this application has been submitted simultaneously, to the relevant National Competent Authorities.** • Date of implementation of the Type IB changes is inserted.		
Grouping is acceptable, either as outlined in Annex III of Reg. (EC) No 1234/2008 or CMDh List of Acceptable Examples or previously agreed with the national competent authority. For purely national variations the grouping complies with BfArM 2nd announcement dated 15 July 2016[10].		
SUPPORTING DOCUMENTATION		
Classification Guideline • **Copy of the relevant page(s) from the Classification Guideline is/are attached for each change applied for or the relevant Art.5 rec. with ticked conditions, if applicable.** This does not apply to changes that are unforeseen in the classification guideline ("z" scopes). • **Relevant conditions and documentation, as specified in the appropriate Guideline[7], are ticked.** A reference, where the appended documents are placed in the submission, should be included.		
Documentation listed in Annex IV of the Variations Regulation and in the Commission Classification guideline. • **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.** • **Reference documents (e.g. PRAC or CMDh recommendation) as applicable should be included in the documentation as well.** • **Correspondence concerning the respective variation with the competent authority, if applicable.**		
PRODUCT INFORMATION (SMPC, LABELLING, PL)		
• **The Product Information (PI) includes only changes declared in the Present and Proposed table in the application form.** • **The PI correctly reflects the scope of the variation and is based on the latest approved version.** • **The PI is provided in all concerned MS languages in Word format (with tracked changes) and as clean PDFs .**		

Type IB submission checklist[2]	Yes	n/a
CHANGES TO THE RMP		
• **The Version number (current and updated) correctly reflected.** • 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).**		
IMPLEMENTATION OF OUTCOME OF A PRAC SIGNAL RECOMMONDATION		
• **The agreed wording is correctly reflected in all applicable sections of the SmPC and PIL as published on the EMA website.** • **Annexes provided in Word version (with tracked changes) and as clean PDF correctly formatted.**		
CHANGES TO AN ASMF		
MAH should submit: • **Application form listing the ASMF version number as well as the relevant version number and/or date in the 'Present and Proposed' table.** In order to avoid validation comments, the national competent authority strongly recommends submission of the variation application once the ASMF holder has successfully carried out the submission of relevant sections of the ASMF in the appropriate eCTD format to the national competent authorities. • **Revised sections of the dossier (open part) corresponding to ASMF open 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)[8,9]. • 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 (open/restricted part) reflecting changes to the previously accepted version, as applicable.**		

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

The checklist is based on the following standards and recommendations

[1] Drawn up in accordance with the pre-notification checklist for type IB variations in the centralized procedure provided by the EMA – see http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500196337

[2] Guidance for submitting variations is provided on the BfArM as well as the CMDh website: http://www.bfarm.de/EN/Drugs/licensing/folgeverfahren/variations/variations/_node.html or http://www.hma.eu/96.html

[3] Please refer to the BfArM eSubmission guidance : http://www.bfarm.de/EN/Drugs/licensing/ZulRelThemen/eSubmission/_node.html

[4] Preferably by using the template http://www.hma.eu/265.html

[5] As published on the Commission's website in Volume 2B of the Notice to applicants.

[6] Please avoid stating 'See Annex A'.

[7] Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01)

[8] Guideline on Active Substance Master File Procedure: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129994.pdf

[9] Additional guidance on documents relating to an ASMF: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133204.pdf

[10] Please refer to BfArM 2nd announcement dated 15 July 2016: https://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/aender/bm-aender-2016-07-15.pdf?__blob=publicationFile&v=2