Bundesinstitut
für Arzneimittel
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Pre-notification check for type IA/IA$_{IN}$ Variations [1]

This pre-notification checklist is aimed at facilitating submission of complete and correct Type IA and Type IA$_{IN}$ 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 IA or Type IA$_{IN}$ 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 Type IA/IA$_{IN}$ variations as minor variations which have only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product and do not require prior approval before implementation ("Do and tell" procedure). Type IA/IA$_{IN}$ variations are reviewed by the national competent authority within 30 days following receipt. These are simple procedures without clock-stop and for which interactions with Applicants are not envisaged.

However, in exceptional cases, the national competent authority may issue a Request for Supplementary Information in exceptions e.g. withdrawn-letter, responses to which should be provided within 4 working days. Failure to respond within the specified deadline may lead to an unfavourable outcome.

For variations classified as Type IA or Type IAIN relating to:

- changes to the Risk Management Plan (RMP)
- implementation of a PRAC signal recommendation wording (when classified as Type IAIN)
- changes to an Active Substance Master File (ASMF)

an additional section of the checklist is presented addressing the specific submission requirements.

Type IA and Type IA$_{IN}$ Pre-notification checklist

Type IA and Type IA$_{IN}$ submission checklist[2]	Yes	n/a
TECHNICAL SUBMISSION REQUIREMENTS		
• Dossier is submitted in eCTD format[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-adress).		
'Type of application' • Correctly identified by ticking the box(es) Type IA, Type IA$_{IN}$. • 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 IA and Type IA_{IN} 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). • The date of implementation is obligatory with dd.mm.jjjj. "Next production run/next printing " is not permitted. The variation has been submitted within 1 year (Type IA) or immediately following implementation (Type IA_{IN}), as appropriate. 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.1 is indicated for each additional new pack size). • 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 IA/IAIN 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".		
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. • 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 .		
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).		

Type IA/IAIN submission checklist[2]	Yes	n/a
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 IA variations in the centralized procedure provided by the EMA – see https://www.ema.europa.eu/documents/other/pre-notification-check-type-ia/iain-variations_en.pdf

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: http://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Arzneimittel/aender/bm-aender-2016-07-15.pdf?__blob=publicationFile&v=2