**Validation Checklist for Type II quality variations**

*Please fill in this checklist and submit it as a word document with your application for type II quality variations*

**Name of the product (invented name):**

**INN/Common name:**

**MAH:**

**eCTD sequence number:**

**Is this application related to a post authorisation measure?** Yes  *If so, please indicate which one /* No

**Procedure Number** *(will be assigned by EMA only upon receipt of an eCTD application and does not need to be included by the MAH at the time of submission)*

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| --- | --- | --- |
| **To be completed by MAH (information provided?)** | | **To be completed by EMA**  **(Comments)** |
| **Is it a type II variation?** | Yes  Please refer to the [Classification of Changes Q&A](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/classification-changes-questions-answers) Question 3 for details on the information that should be submitted as a type II variation. |  |
| **Variation category:** | *Please refer to the variation scope laid down in the ‘*[*Variations Guidelines*](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:223:FULL:EN:PDF)*’ or reference to the* [*published Article 5 recommendation*](https://www.hma.eu/293.html)*”* |  |
| **Proposed scope(s)** | *Please refer to the ‘*[*Guidance for applicants for the preparation of the precise scope section of the variation application form*](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-applicants-preparation-precise-scope-section-variation-application-form_en.pdf)*’ and Q&A 3.6* <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/classification-changes-questions-answers>*.*  *In case of grouping each scope should be clearly listed and adequate level of detail provided for each one.*  *Please refer also to* [*Classification of Changes Q&A*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/classification-changes-questions-answers) *(Quality changes)* |  |
| **Do the data submitted qualify as more than one scope (i.e.: is this a** [**Grouping of Variations**](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/grouping-variations-questions-answers)**)?** | Yes  *If yes, please consider the* [*specific conditions and requirement*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/grouping-variations-questions-answers)*s that would apply.*  No  *In case of addition of new presentation(s), one scope per new presentation should be included.*  *In case of additions of new manufacturing/QC testing sites one scope per new site should be included.* |  |
| **Is this a** [**Worksharing application**](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/worksharing-questions-answers)**?** | Yes  No |  |

| **Module** | **Component** | **Guidance (in line with** [**the post authorisation guidance published on EMA website**](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/type-ii-variations-questions-answers)**)** | **MAH** | **EMA** |
| --- | --- | --- | --- | --- |
| 1 | Cover letter | *For* ***groupings****, include a short overview of the nature of the changes and indicate whether it is submitted under Article 7.2(b) i.e. it falls within one of the cases listed in Annex III of the variations regulation or it is submitted under Article 7.2.(c) i.e. the grouping has been agreed with the Agency. For guidance on groupings, please refer to the* [*Q&A published on the EMA website*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/grouping-variations-questions-answers)*.*  *For* ***worksharing******variations****, please ensure that the requirements described in the* [*Q&A*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/worksharing-questions-answers) *are met, in particular: all changes/variations should apply to all products, confirmation that all products belong to the same holder, confirmation and Letter of Authorisation as relevant for the signatory to act as the contact person for the WS procedure. If NAPs are included in the WS procedure, confirmation that the application has been submitted to all concerned MSs, fees paid and Annex B (listing all NAPs) included in module 1.2.*  *If applicable, the MAH may provide relevant documents as attachments to the cover letter, e.g. Agency requests for variations implementing changes for generic/hybrid/biosimilar medicinal products, CHMP PAM assessment reports, PRAC PSUSA assessment reports and Scientific Advice letters etc.* |  |  |
| 1.2 | Completed and signed electronic EU variation application form (eAF) | *Including the details of the marketing authorisation(s) concerned.*  *Reference to the variation scope laid down in the ‘Variations Guidelines’ or reference to the published* ***Article 5*** *recommendation, if applicable, should be made.*  *In case of* ***groupings*** *the corresponding classification scopes should be indicated as many times as needed taking into account that one classification scope is to be indicated per variation.*  *Where a variation leads to or is the consequence of other variations, a description of the relation between these variations should be provided in the appropriate section of the application form. All proposed changes should be declared in the ‘Type of changes’ section of the form, and clearly described in the ‘scope’ section of the form.*  *The ‘****present/proposed’*** *section in the application form should reflect all proposed changes to Modules 2, 3 and the English Product Information (SmPC, Annex II, labelling and package leaflet) as current and proposed text. Alternatively, if the proposed changes are extensive the applicant may instead provide the ‘present/proposed’ comparison as part of a separate annex to the application form. In this case, the applicant should include in the ‘present/proposed’ section of the application form a cross-reference to this annex.*  ***Editorial changes*** *should also be included in the present/propose table and justify the change as editorial.*  *Please refer also to* [*Classification of Changes Q&A*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/classification-changes-questions-answers) *(Editorial changes)* |  |  |
| 1.2 | Attachments to the eAF (e.g. GMP compliance documents) | *The variation concerns* ***addition of manufacturing or QC testing sites*** *for the active substance or the finished product.*  *For addition of new manufacturing sites (active substance or finished product, including QC sites), please provide:*  *- Module 1.2: Application Form (precise scope and details of variation, and present/proposed table; type of testing should be specified for QC testing sites; if a site is conducting QC testing for the purpose of batch release in the EEA, this should be clearly stated).*  *- 5.8 (flow-chart)*  *- Module 3: sections 3.2.S.2.1 and /or 3.2.P.3.1 as applicable*  *The details regarding full name and address of the site as well as manufacturing activities performed should be consistent across the AF (precise scope, present/proposed table), flow chart, module 3 and the GMP documentation provided (MIA or equivalent, GMP certificate).*  *In the present/proposed table, the* ***new site must be selected from SPOR/OMS*** *to autofill address details [the new site must be registered in OMS before the variation is submitted].*  *In addition, for a new active substance manufacturing site (chemical active substance):*  *- 5.22 (QP declaration)*  *In addition, for a new active substance manufacturing/testing site (biological active substance):*  *- 5.22 (QP declaration)*  *- 5.9: proof of GMP compliance*  *In addition, for a new manufacturer of the finished product (including QC sites):*  *- 5.6: proof that the site is appropriately authorised (proof of GMP compliance may suffice for QC sites)*  *- 5.9: proof of GMP compliance if the site is located outside the EEA*  *- 5.22 (QP declaration) if the manufacturer is located in the EEA and using the active substance as a starting material (also if the site is responsible for batch certification)*  *For proof of GMP compliance: copy of GMP certificate issued by EEA authority or EudraGMDP reference number for sites located in the EEA or in third countries. Copy of GMP certificate issued by local competent authority for sites located in MRA countries (*<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra>*).*  *For manufacturing sites located in the USA see here:* <https://www.ema.europa.eu/en/documents/other/questions-answers-impact-european-union-united-states-mutual-recognition-agreement-marketing_en.pdf>*.*  *The absence of sufficient proof of GMP compliance may trigger an inspection. If the manufacturing site may require an inspection, based on absence of GMP compliance statement or other criteria, please liaise with EMA around 3 months prior to the planned variation submission to allow time to organise the inspection, if needed.*  *To confirm authorisation of a finished product manufacturer: copy of MIA or EudraGMDP reference number for sites located in the EEA. Authorisation issued by local competent authority for sites located outside the EEA. For sites located in the USA, a screenshot from the FDA drug establishments current registration website can be accepted:* <https://www.accessdata.fda.gov/scripts/cder/drls/default.cfm>  *The absence of sufficient proof of authorisation may block validation of the variation.* | N/A |  |
| 1.3.1 | Product information | *In case changes to the PI are proposed, a revised full set of annexes (SmPC, Annex II, labelling and package leaflet) should be provided in English.*  *The application must include word clean and highlighted versions of the annexes, clearly showing all proposed amendments in track changes.*  *The clean version should be provided as a PDF document in module 1.3.1 and a highlighted version should be submitted as a word document as part of the ‘working documents’ outside the eCTD structure.*  *Please also refer to Question 16 “*[*When do I have to submit revised product information? In all languages*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/type-ii-variations-questions-answers)*?”.* | Highlighted Word version provided\*:  N/A |  |
| **Annex A** | New Presentations | *Any changes in the number of units of* [*medicinal product*](https://www.ema.europa.eu/en/glossary/medicinal-product) *or medical device being an integral part of the medicinal product (e.g. prefilled syringes) will trigger a different EU number.*  *New presentations need to be correctly inserted in Annex A (include a draft Annex A) and in the Product Information.* | N/A |  |
| 1.4.1 | Information about the quality expert (Signed and dated expert statement + CV) | *Mandatory for all type II variations including or referring to quality data. The quality expert is accountable for quality overview/addendum.*  (Signed & dated expert statement + CV) |  |  |
| 1.8.2 | Risk management Plan | *If applicable with revision date and version number or justification if not considered necessary. The justification, where applicable, should be included in module 1.8.2 or alternatively in the cover letter and/or the quality overview.*  *When an updated RMP is proposed, the application should include both a clean and highlighted version of the revised RMP, clearly showing all proposed changes in track changes. All parts and modules of the clean RMP should be submitted in one single PDF-file.*  *The highlighted version should also be provided as a word document in the ‘working documents’ outside the eCTD structure (see below).*  *Please also refer to “*[*Risk Management Plan (RMP): questions and answers*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/risk-management-plan-rmp-questions-answers)*”.* | Word version provided\*:    N/A |  |
| 2.3 | Update or addendum to the quality overview | *A quality overview /addendum is mandatory for all quality type II variations.* | Word version provided\*:    N/A |  |
| 3 | Quality | *Relevant sections should be provided* |  |  |
| ASMF | **Changes to ASMF** | *The MAH should submit:*  *• Application form listing the ASMF number in the ‘Present and Proposed’ table (last row). In order to avoid validation comments, the EMA strongly recommends submission of the variation application once the ASMF holder has requested and obtained an EU or EMA ASMF reference number and has successfully carried out the submission of relevant sections of the ASMF in the appropriate eCTD format. Please, note there are two types of ASMF numbers:*  *# an EMA ASMF number (e.g EMA/ASMF/XXXXX)*  *-> in this case the usual process should be followed.*  *# an EU ASMF number (e.g EU/ASMF/XXXXX)*  *-> in this case the ASMF will fall under a procedure called ASMF worksharing that allows Member States to share the assessment report for the same version of the ASMF submitted in CP, DCP or MRP marketing authorisation applications and variation applications. If an EU ASMF number already exists, an EMA ASMF number should not be requested).*  *• 3.2.S corresponding to revised sections of the dossier which should correspond to the ASMF Holder’s Open Part.*   * *3.2.S corresponding to revised section of the dossier which should correspond to additional information and data to assure the quality control of the active substance by the finished product manufacturer (if applicable).*   *(There should be as many 3.2.S sections as manufacturers and Active Substances)*  *Please refer to Q.3.3.5 of the Pre-submission guidance How shall I submit an Active Substance Master File (ASMF)?*  [How shall I submit an Active Substance Master File (ASMF)?](https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance#3.3-quality-section)  [Guideline on Active Substance Master File Procedure](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-active-substance-master-file-procedure-revision-3_en.pdf)  [Additional guidance on documents relating to an active substance master file](https://www.ema.europa.eu/en/documents/scientific-guideline/additional-guidance-documents-relating-active-substance-master-file_en.pdf)  *The MAH should liaise with the ASMF Holder to ensure that the following documentation is submitted:*  *• Letter of Access and administrative details (Annex 3 of the ASMF Guideline).*  *• 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.* | N/A |  |
| Changes to CEP (when included as part of a grouping in Type II variations) | CEP | *The MAH should submit:*  *• Application form listing the revision and version numbers\* of the CEP in the ‘Present and Proposed’ table plus any other changes that the new/updated CEP could bring.*  *\*Each CEP version requires a separate scope (variation), if used in the production of the finished product. In case a certain CEP version was not used in production, the MAH should mention this in the eAF as for skipped (not implemented) CEP versions separate scope is not required. In order to avoid validation comments, the latest CEP version should be submitted according to the information published on* <https://extranet.edqm.eu/publications/recherches_CEP.shtml>, *otherwise, a justification should be included on why the latest CEP is not provided (i.e. the latest version is not yet implemented in production).*  *Updated 3.2.R including the updated CEP*  *• Revised sections of the dossier with the following structure:*  *(1) module 3.2.S from the active substance manufacturer(s) per active substance. (All documents in modules “3.2.S.x.x” should be submitted stating the CEP number only when the relevant section is covered by the CEP.) Mandatory modules to be submitted 3.2.S.2.1, 3.2.S.4.1, 3.2.S.4.4 and 3.2.S.7 (if no retest period is stated on the CEP and the MAH does not test upon receipt the active substance)*  *(2) module 3.2.S from the finished product manufacturer(s) per active substance. (Data to assure the quality control of the active substance by the finished product manufacturer, if different from the CEP .)* | N/A |  |
| 3.2.R | Medical Device | * ***Integral****: the* [*medicinal*](https://www.ema.europa.eu/en/glossary/medicinal-product) *product* *and device form a single integrated product;* * ***Co-packaged****: the* [*medicinal*](https://www.ema.europa.eu/en/glossary/medicinal-product) *product* *and the device are separate items contained in the same pack.* * ***Devices referenced in the product information***   *Applicant should refer to guidance available on the webpage on* [Medical Devices](https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices) | N/A |  |
| **To be completed by EMA only:** Valid variation application? | | | | Yes  No |
| If no, comments: | | | |  |

\*Working documents outside the eCTD structure: Additional Word formats of certain documents are required to facilitate the assessment i.e. ‘tracked changes’ versions for SmPCs, RMPs or other documents specified by the Agency (e.g. summary of efficacy table for extension of indications). These should be provided in the separate folder ‘XXXX-working documents’. Further details can be found in the Harmonised Guidance for eCTD Submissions in the EU. It is generally not necessary to include the RMP annexes in the ‘working document’ version (unless annexes are being revised).