**Validation Checklist for Type II (non)clinical variations**

*Please fill in this checklist and submit it as a word document as part of the working documents with your application for type II clinical, non-clinical and RMP 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** | | **To be completed by EMA** |
| **Is it a type II variation?** | Yes *Please refer to the* [*Classification of changes: questions and answers*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/classification-changes-questions-answers) *Question* [3](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-measures-questions-answers) *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)*’* |  |
| **Proposed scope:** | *Template wordings for the more frequent variation scopes are provided below as guidance:*  ***C.I.4, C.I.3, C.I.6 (non-Extension of Indication):*** *Update of section<s> X, X, and X of the SmPC in order to <introduce a new posology regimen>, <change posology recommendations in…>, <modify administration instructions>, <add a new contraindication>, <change an existing contraindication>, <add a new warning on…>, <amend an existing warning on…>, <add drug-drug interaction information with…>, <update information on pregnancy>, <add (term) to the list of adverse drug reactions (ADRs) with frequency (frequency category)>, <update the description of…>, <update efficacy, pharmacokinetic, non-clinical information…> following (refer to prior regulatory procedure/outcome)/based on…<(interim/final) results from study…(include study identifier)**listed as a specific obligation/imposed PASS/obligation/PAES in the Annex II/ a category 3 study in the RMP; this is a (include a high-level description of the study so as to clarify whether the study is interventional or observational and whether the primary objective relates to efficacy or safety; this is in most cases obvious from the study description)*>; *<the Package Leaflet <and Labelling> are updated accordingly.>< The RMP version X has also been submitted.> <In addition, the <MAH/WSA/SOH> took the opportunity <to update the list of local representatives in the Package Leaflet> <and> <to bring the PI in line with the latest QRD template version Y.y>.*  ***C.I.6 (Extension of indication):*** *Extension of indication to include <in combination with...> treatment of <new indication/population> for <PRODUCT NAME>, based on…<(interim/final) results from study…(include study identifier); this is a (include a high-level description of the study so as to clarify whether the study is interventional or observational and whether the primary objective relates to efficacy or safety; this is in most cases obvious from the study description)>; As a consequence, section<s> X, X, and X of the SmPC are updated. <The Package Leaflet <and Labelling> is/are updated in accordance.> <Version X of the RMP has also been submitted.> <In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.> <Furthermore, the PI is brought in line with the latest QRD template version Y.y. >*  ***C.I.13:*** *Submission of the final report from study/studies (include study identifier(s)) <listed as a category 3 study in the RMP>. This is a… (include a high-level description of the study so as to clarify whether the study is interventional or observational and whether the primary objective relates to efficacy or safety; this is in most cases obvious from the study description).<The RMP version X has also been submitted.>*  ***C.I.11 for RMP:*** *Submission of an updated RMP version X in order to (describe main changes).*  ***C.I.11 for ANX or SOB studies:*** *Submission of the final report from study/studies (include study identifier(s)) listed as a Specific Obligation/an obligation in the Annex II of the Product Information. This is a… (include a high-level description of study as explained above). The Annex II <and the RMP (version X)> are updated accordingly.* |  |
| **Is the target population being extended?** *(see* [*Qu*estion *3.6*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/classification-changes-questions-answers)*)* | Yes  *If yes, please consider that paediatric and orphan requirements will have to be addressed (see* [*Que*stions *20 and 24*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/type-ii-variations-questions-answers)*)*  No |  |
| **Is it a new or modified therapeutic indication?** | Yes  *If yes, please also provide the information grey shaded in the checklist below.*  No |  |
| **Do the data submitted qualify as a 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 |  |
| **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** |
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| 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*](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***](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/grouping-variations-questions-answers) *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.*  *Please note that filling in the* ***Present/Proposed table*** *is mandatory for any changes proposed to the Product Information, highlighting (underline and/or strike-through) the changed wording applied for. Alternatively, the Present/Proposed table can be uploaded as a separate Annex to the application form if preferred.* |  |  |
| 1.3.1 | Product information (PI) | *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 |  |
| 1.3.4 | User testing | Consultation with target patient groups (user testing results) or a justification why this was not considered necessary should be provided |  |  |
| 1.4.2 | Information about the non-clinical expert | *Mandatory for all type II variations including or referring to non-clinical data. The non-clinical expert is accountable for the non-clinical overview/addendum*  (Signed & dated expert statement + CV) | N/A |  |
| 1.4.3 | Information about the clinical expert | *Mandatory for all type II variations including or referring to clinical data and/or applications including an updated version of the Risk Management Plan (RMP). The clinical expert is accountable for the clinical overview/addendum*  (Signed & dated expert statement + CV) | N/A |  |
| 1.5.3 | Additional year of market/data protection | *When the applicant requests consideration of an additional year of market protection in accordance with Article 14(11) of Regulation (EC) No 726/2004 or an additional year of data protection in accordance with Article 10(5) of Directive 2001/83/EC, a report should be provided in this module. For further details on the content of the report, reference should be made to Eudralex Volume 2B for the Commission ‘*[*Guidance on elements required to support the significant benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11 years) marketing protection period*](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf)*’ or ‘*[*Guidance on a new therapeutic indication for a well-established substance*](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/10%2520_5_%2520guideline_11-2007_en.pdf)*’.* | N/A |  |
| 1.6 | Environmental Risk Assessment (ERA) | *Expert assessment with or without study report(s) or justification why not considered necessary and the CV and signature of the expert should be provided for all type II variation applications under category C.I.6.a.* |  |  |
| 1.7.1 | Similarity assessment | *As applicable. Refer to Question 20* [*'What aspects should I consider at time of submission of a type-II variation if there are orphan medicinal products designated or authorised for a condition related to my proposed therapeutic indication?*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/type-ii-variations-questions-answers)*'* | N/A |  |
| 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 clinical overview.*  *Please note that an updated RMP (with revision date and version number) or justification - if not considered necessary – should be provided for a new or modified therapeutic indication.*  *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).*  *MAHs are requested to provide high-level explanation of the changes proposed to the RMP either in the Cover Letter or the Application Form.*  *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 |  |
| 1.9 | Information relating to Clinical Trials | Statement indicating that clinical trials conducted outside the EU meet the ethical requirements of Directive (EC) No 2001/20/EC or Clinical Trials Regulation (Regulation (EU) No 536/2014), as applicable, together with a listing of all trials (protocol numbers), and third countries involved.  *This statement is required when clinical trial reports are submitted for studies with at least one study site outside the EU. This requirement does not apply for non-interventional studies.* | N/A |  |
| 1.10 | Paediatric information | *Please refer to Question 24* [*https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/type-ii-variations-questions-answers*](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/type-ii-variations-questions-answers) |  |  |
| 2.4 | Update or addendum to the non-clinical overview | *A non-clinical overview /addendum is mandatory for all non-clinical type II variations regardless of the impact on the PI. The document should discuss the data provided, address the impact on the PI and/or the RMP (if any), and conclude on the impact on the overall benefit/risk balance.* | Word version provided\*:  N/A |  |
| 2.5 | Update or addendum to the clinical overview | *A clinical overview/addendum is mandatory for all clinical type II variations regardless of the impact on the PI. The document should discuss the data provided, address the impact on the PI and/or the RMP (if any), and conclude on the impact on the overall benefit/risk balance. It should be noted that a clinical overview/addendum is mandatory also for type II variations that only concern an update of the RMP.* | Word version provided\*:  N/A |  |
| 2.6 | Non-clinical Summary(ies) | *Whenever non-clinical study reports are provided, even if only one, relevant non-clinical summary(ies) are mandatory.* | Word version provided\*:  N/A |  |
| 2.7 | Clinical Summary(ies) | *Whenever clinical study reports for interventional studies are submitted, even if only one, relevant clinical summary(ies) are mandatory. However, it should be noted that summaries are not required for non-interventional studies.* | Word version provided\*:  N/A |  |
| 4 | Non-Clinical Study Reports | Supporting non-clinical data/study reports relating to the proposed variation(s), including literature references, should be provided. *Have relevant non-clinical data (eCTD 4.2) or literature references (eCTD 4.3) been submitted to support the intended change(s)-variation(s)?* | N/A |  |
| 5 | Clinical Study Reports | Supporting clinical data/study reports relating to the proposed variation(s), including literature references, should be provided. *Have relevant clinical data (eCTD 5.3) or literature references (eCTD 5.4) been submitted to support the intended change(s)-variation(s)?* | N/A |  |
| 5.2 | Tabular Listing of all Clinical Studies | This listing should be updated when new studies are submitted | N/A |  |
|  | Appendices to clinical study reports | Please refer to [CHMP/EWP/2998/03/Final](https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-inclusion-appendices-clinical-study-reports-marketing-authorisation-applications_en.pdf) | 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 and RMPs, ‘clean’ versions of all documents provided in Module 2 (Non-clinical and Clinical Overviews, relevant Summaries), and other documents specified by the Agency (e.g. summary of efficacy table for extension of indications). These should be provided in Word format 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).