EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

Pre-submission checklist for type II variation applications

The purpose of this checklist is to facilitate submission of complete and correct type II variation applications by marketing authorisation holders (MAHs)

Guidance for Marketing Authorisation Holders

The Agency strongly recommends that this checklist is used in advance of submission of type II variation applications. 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.

Upon receipt of a type II variation application, the procedure manager proceeds to validate the documentation submitted in accordance with the checklist included below. The validation elements which would prevent the start of the procedure until they are addressed satisfactorily are presented in ***bold italics***. Please note that certain blocking elements are only specified in the guidance in ***green bold italics***. Remaining elements facilitate either validation or assessment and related issues can be communicated during validation to help improve future submissions but will not block validation.

Issues identified during validation will be notified to the MAH via email. The MAH will be requested to provide responses to the issues raised. Delayed or insufficient responses may affect the timely start of the procedure (for information related to assessment timelines please refer to the relevant procedural timetables).

Reference documents for further information:

- Variation Regulation (EC) No 1234/2008
- Variations guidelines
- Post-authorisation guidance on classification of changes
- Post-authorisation guidance on type II variations
- Post-authorisation guidance on RMP updates
- Post-authorisation guidance on grouping of variations
- Post-authorisation guidance on worksharing

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Type II variation – validation checklist

Module 1

1.0 Cover letter	Yes	No	N/A	Comments
Cover letter submitted?	☐	☐		

1.2 Application form	Yes	No	N/A	Comments
Application form submitted (current version to be found here)	☐	☐		
1.2 Application form section 1 ***Name and address of the MAH as previously notified to the Agency***	☐	☐		
Application form signed by the authorised contact person (or letter of authorisation is provided)	☐	☐		
1.2 Application form section 2 EU numbers of all affected presentations are listed	☐	☐		***Mandatory for certain quality variations pertaining only to a subset of presentations***

1.2 Application form	Yes	No	N/A	Comments
1.2 Application form section 3 Precise scope ***The proposed changes correspond to one (or more) type II variation scopes (as opposed to other application types: line extension, IA or IB variation, 61(3) notification, PAM, PASS 107n,o,q)***	☐	☐		
The change is correctly classified (correct scope category based on the Annex of the Variations guidelines; single variation)	☐	☐		
Precise scope is complete and clearly describes the change applied for (please consider guidance on how to write scopes)	☐	☐		
The variation triggers new pack sizes/new presentations	☐	☐		*Each new EU number triggers one scope/fee. The main Type II change (e.g. to add new*

1.2 Application form	Yes	No	N/A	Comments
				device) covers 1 presentation. Additional pack sizes should be submitted under additional B.II.e.5.a) scopes. The Annex A should be updated accordingly.
For grouped variations with many scopes (particularly quality), the precise scope is broken down per scope classification	☐	☐	☐	
When PI is affected the sections of the SmPC are mentioned and QRD-related updates, editorial updates, changes to local representatives are specified	☐	☐	☐	
Origin of changes is mentioned (e.g. reference to data previously submitted and assessed as part of PAM/PSUR or post-marketing reports, clinical studies etc.)	☐	☐		
In case of RMP update, the version number is specified and the main changes are described	☐	☐	☐	
For submission of study reports scope includes 1) study identifier(s) 2) category in the RMP if applicable and 3) high-level description of study	☐	☐	☐	

1.2 Application form	Yes	No	N/A	Comments
1.2 Application form section 3 Precise scope - Extension of indication Are the PI changes extending the target population i.e. extension of indication?	☐	☐		*Note that this could include PI changes which do not affect SmPC 4.1 (refer also to the relevant question under (Non) Clinical changes in the Classification of changes)* ***If Yes, please fill out items related to section 4 of the application form*** *If No please ignore checklist items related to section 4 of the application form*

1.2 Application form	Yes	No	N/A	Comments
1.2 Application form section 3 Precise scope - Grouping and worksharing				*If no grouping or worksharing applies, then please move to the next section of the*

1.2 Application form	Yes	No	N/A	Comments
If no grouping or worksharing is proposed, do all propose changes fall under a single scope?	☐	☐		*application form*
Is grouping acceptable (for information on acceptable groupings please follow the link)?	☐	☐		
Is the number and category of scopes corresponding to the number and type of changes?	☐	☐		
If type IA are included in the grouping: All Type IA_{IN} are submitted immediately following implementation	☐	☐	☐	
Date of implementation of oldest Type IA is within 1 year of submission of the application	☐	☐	☐	
Worksharing: all the variations apply to all products concerned	☐	☐		
Worksharing: explanation that all products concerned belong to the same holder	☐	☐		
Confirmation that the worksharing application has been submitted to all MSs concerned and that the relevant fees have been paid, if MRP products are part of the worksharing	☐	☐		
Annex B listing all NAPs included in the worksharing	☐	☐	☐	
Confirmation that the signatory is contact person for worksharing procedure (Application form or letter with applicant and contact person for worksharing procedure in module 1.2)	☐	☐		

1.2 Application form	Yes	No	N/A	Comments
1.2 Application form section 4a **For orphan medicinal products: *is the proposed indication within the scope of an orphan designation?***	☐	☐		*If the proposed indication falls partially within the scope of an orphan designation, the indication will need to be restricted to fully fall within the orphan designation; alternatively or if the proposed is within a non-orphan condition, the MAH must withdraw the orphan designation at the latest 2 days after receipt of positive CHMP Opinion;*
If yes, has the MAH submitted a report to COMP supporting the maintenance of the orphan designation?	☐	☐		*Report or justification for the lack thereof should be submitted for ANY extension of indication to orphandrugs@ema.europa.eu*
For ALL medicinal products: ***Is there any orphan product(s) authorised in the EEA/EU for a condition linked to the proposed indication?***	☐	☐		*If yes, then a similarity report should be included in module 1.7.1 and a separate AR assessing the request will be circulated by the Rapporteur(s).*
Is the medicinal product, subject of this application, considered as "similar" to any of the authorised orphan medicinal product(s)?	☐	☐		*If yes, then a report on derogations should be included in module 1.7.2 and a separate AR assessing the report will be circulated by the Rapporteur(s).*

1.2 Application form	Yes	No	N/A	Comments
1.2 Application form section 4b ***Paediatric requirements applicable?***	☐	☐		

1.2 Application form	Yes	No	N/A	Comments
1.2 Application form section 4c Extended data exclusivity/market protection claims submitted?	☐	☐		***If yes, then supporting documentation should be submitted in module 1.5.3***
One year of market protection for a new indication (Article 14(11) of Regulation (EC) No 726/2004 and Article 10(1) of Directive 2001/83/EC)	☐			
One year of data exclusivity for a new indication for a well-	☐			

1.2 Application form	Yes	No	N/A	Comments
established substance (Article 10(5) of Directive 2001/83/EC)				
One year of data exclusivity for a change in classification (Article 74(a) of Directive 2001/83/EC)	☐			

1.2 Application form	Yes	No	N/A	Comments
1.2 Application form – remaining items Present/Proposed table or attachment reflects all PI and/or RMP changes applied for, dossier section numbers refer to the lowest possible level and include the precise current and proposed wording.	☐	☐	☐	*If PI and RMP changes are extensive, cross-reference to the highlighted document can be included* *For Quality variations, all module 3 changes should be detailed in the table*
Correct boxes crossed for the changes in PI	☐	☐	☐	

1.3 Product Information	Yes	No	N/A	Comments
1.3.1 SmPC, Labelling and PL	☐	☐	☐	*If n/a, please move to the next section*
Full set of Annexes in English Highlighted	☐	☐		***Required only in case the Product Information is amended;*** *clean PI should be submitted in eCTD Module 1.3.1 (highlighted PI should also be included in eCTD, if changes are not specified in the Present/Proposed table or presented in an Annex to the application form)* *Highlighted version should also be provided as a word document as part of the 'working documents' outside the eCTD structure*
Affected Annexes:				
Annex A	☐	☐		
Annex I –SmPC	☐	☐		*For a newly proposed combination of SmPCs: 1) the primary pharmaceutical form should be the same e.g. solution for injection in vial and solution for injection in pre-filled syringe can be combined 2) the SmPCs must be fully identical to the exclusion of minor strength-specific details, e.g. if the indications are different for the different strengths, the SmPCs*

1.3 Product Information	Yes	No	N/A	Comments
				cannot be combined (for more information please refer to the relevant policy).
Annex II	☐	☐		
Annex IIIA –Labelling	☐	☐		
Annex IIIB –PL	☐	☐		*A newly proposed combination of Package Leaflets should always be endorsed by the QRD plenary.*
Annex IV	☐	☐		*Annex IV from previous procedures should be removed at the time of submission of the variation.*
Annex 127a	☐	☐		
Implementation of the latest QRD template	☐	☐		
Document in support of addition/change of QR code	☐	☐		*Please refer to relevant guidance.*
1.3.2 Mock-ups	☐	☐	☐	*Mock-ups are expected in cases of changes triggering new presentations where layout could be affected (e.g. new administration device/pen/pre-filled syringe, new initiation pack)*
1.3.3 Specimens	☐	☐	☐	*For the requirements for submission of specimens in case of post-authorisation procedures other than renewals, transfers and extensions of MA refer to the guidance on the checking process of mock-ups and specimens in the centralised procedure*
1.3.4 Consultation with Target Patient Groups or justification for not performing such consultation	☐	☐	☐	***Expected only in case of significant changes to the PL, e.g. as part of extension of indication***

1.4 Information about the experts	Yes	No	N/A	Comments
1.4.1 Quality expert signed statement + CV	☐	☐	☐	***Required only for Quality variations;*** *the signed statement should be in line with the template from NTA Volume 2B*
1.4.2 Non-clinical expert signed statement + CV	☐	☐	☐	***Required only for Non-clinical variations;*** *the signed statement should be in line with the template from NTA Volume 2B*
1.4.3 Clinical expert signed	☐	☐	☐	

1.4 Information about the experts	Yes	No	N/A	Comments
statement + CV				***Required only for Clinical variations;*** *the signed statement should be in line with the template from NTA Volume 2B*

1.5.3 Extended Data exclusivity/Market protection	Yes	No	N/A	Comments
Documentation supporting the request submitted?	☐	☐		***Applicable only if a relevant request has been submitted as indicated in section 4c of the application form; otherwise N/A***

1.6 Environmental Risk Assessment	Yes	No	N/A	Comments
Expert assessment with or without technical dossier (study reports) or justification, if applicable (e.g. new indication).	☐	☐	☐	***Applicable only for Extension of Indications; otherwise N/A***
Expert identified with signature, date & CV	☐	☐		***Applicable only if an updated ERA or justification for the lack thereof is submitted; otherwise N/A***

1.7 Orphan Market Exclusivity	Yes	No	N/A	Comments
1.7.1 Report on similarity	☐	☐	☐	***Applicable for all Extensions of Indications; otherwise N/A***
1.7.2 Report on derogations	☐	☐		***Needed if product is considered similar in 1.7.1***

1.8.2 Risk-Management Plan	Yes	No	N/A	Comments
Risk Management Plan submitted?	☐	☐		***If no RMP updated is proposed in case of an extension of indication, a justification must be provided*** *For the requirements for the RMP submission please refer to the relevant guidance*
Are all proposed changes to safety concerns, PhV plan and risk minimisation measures consequential to the variation scope or already agreed in previous regulatory	☐	☐		*If not, then additional type II variation scopes (C.I.11.b) should be triggered. Please note that changes previously agreed only in principle, but supported by additional data/requiring significant assessment, trigger*

1.8.2 Risk-Management Plan	Yes	No	N/A	Comments
procedures?				*additional C.I.11.b scopes*

1.9 Clinical trials statement	Yes	No	N/A	Comments
Statement indicating that Clinical Trials conducted outside the EU meet the ethical requirements of Dir. 2001/20/EC, together with a listing of all trials (protocol numbers), and third countries involved submitted? (relevant when clinical trial reports are submitted)	☐	☐	☐	*Applicable when a clinical study(ies) has/have been conducted outside the EU.*

1.10 Information regarding paediatrics	Yes	No	N/A	Comments
Application for a new indication (including paediatric indication)?	☐	☐	☐	
Is the latest Agency Decision on a PIP / product-specific waiver / class waivers with its annexes submitted in Module 1.10?	☐	☐	☐	
Agency Decision Number on a PIP / product-specific waiver / class waivers	<Insert decision number here>			
List below ALL indications, pharmaceutical form(s) and route(s) of administration applied for, the corresponding condition, and whether the indications, pharmaceutical form(s) and route(s) of administration are covered by the condition(s) in the latest Agency's decision or not:				
Indication(s) as applied for in the SmPC:	☐	☐	☐	Condition as per latest Agency Decision: Is the indication(s) covered by the condition(s) in the latest Agency's decision?
Pharmaceutical form(s) as applied for in the SmPC:	☐	☐	☐	Pharmaceutical form(s) as per latest Agency Decision: Is the pharmaceutical form(s) covered by the latest Agency's decision?

1.10 Information regarding paediatrics	**Yes**	**No**	**N/A**	**Comments**
Route(s) of administration as applied for in the SmPC	☐	☐	☐	Route(s) of administration as per latest Agency Decision: Is the route(s) of administration covered by the latest Agency's decision?

1.10 Information regarding paediatrics – Compliance check	**Yes**	**No**	**N/A**	**Comments**
Is this PIP eligible for the reward?	☐	☐	☐	<Insert decision number for the PIP eligible for the reward:>
If all studies/measures are due at the time of submission is there a compliance report and positive compliance Opinion submitted in Module 1.10?	☐	☐	☐	*If Yes move to next question.* *If No list this validation issue as it should appear in the VSI.* *Select n/a in case of a waiver where no measures will be requested.*
If at least 1 study/measure is due at the time of submission is there a compliance report and partial compliance check letter submitted in Module 1.10?	☐	☐	☐	*If Yes move to next question.* *If No list this validation issue as it should appear in the VSI.* *Select n/a in case of a waiver where no measures will be requested.*
Are additional measures due since the date of the compliance check?	☐	☐	☐	*If Yes list this validation issue as it should appear in the VSI.* *If No move to next question.*
Is the same data submitted in Module 4 (Non-clinical study reports) as during the compliance check?	☐	☐	☐	*If No list this validation issue as it should appear in the VSI.* *N/A means that no data is required.*
Is the same data submitted in Module 5 (Clinical study reports) as during the compliance check?	☐	☐	☐	*If No list this validation issue as it should appear in the VSI.* *N/A means that no data is required.*

Module 2 – Overviews & Summaries	**Yes**	**No**	**N/A**	**Comments**
2.3 Quality overall summary	☐	☐	☐	
2.4 Non-Clinical Overview	☐	☐	☐	
2.5 Clinical Overview	☐	☐	☐	
2.6 Non-Clinical Summary	☐	☐	☐	***Whenever non-clinical study reports are provided, even if only one, relevant non-clinical summary(ies) are mandatory.***
2.7 Clinical Summary	☐	☐	☐	***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 studies not covered in the Notice to Applicants***
Is the submitted module 2 documentation (i.e. overview, summary) adequately supporting the proposed changes?	☐	☐		

Module 3 – Quality	**Yes**	**No**	**N/A**	**Comments**
Quality area affected?	☐	☐		*If not, please move to the next section*
Sections listed in present/proposed table present?	☐	☐		
For Type IA, IB: Documentation as per guideline provided for each change applied for?	☐	☐	☐	

Module 4 – Non-Clinical Study Reports	**Yes**	**No**	**N/A**	**Comments**
Non-clinical area affected?	☐	☐		*If not, please move to the next section*
4.2.1 Pharmacology data	☐	☐		
4.2.2 Phamacokinetics data	☐	☐		
4.2.3 Toxicology data	☐	☐		
4.3 Literature references	☐	☐		

Module 5 – Clinical Study Reports	**Yes**	**No**	**N/A**	**Comments**
Clinical area affected?	☐	☐		*If not, please move to the next section*
5.2 Tabular listing of Clinical studies	☐	☐		
5.3 Clinical data	☐	☐		
5.4 Literature References	☐	☐		

Clinical study report section 16.1 Study information	**Yes**	**No**	**N/A**	**Comments**
Clinical study reports submitted?	☐	☐		***For Variations containing new clinical study report(s) in module 5.3: The following Appendices are required to be submitted (for guidance please refer to CPMP/EWP/2998/03/final)*** ***Appendices will be checked only for the pivotal clinical study report(s) submitted as part of extensions of indications; otherwise N/A***
1. Protocol and protocol amendments	☐	☐		
2. Sample case report form	☐	☐		
3. List of IECs (Independent Ethics Committees) or IRBs (Institutional Review Boards)	☐	☐		
4. List and description of investigators and other important participants in the study	☐	☐		
5. Signature of principal or coordinating investigator	☐	☐		
6. Randomisation scheme and codes	☐	☐		
7. Audit certificates (if available)	☐	☐		
1. Protocol and protocol amendments	☐	☐		
2. Sample case report form	☐	☐		

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 to be addressed by the MAH.

Elements to be considered for the choice of timetable

Foreseen immediate CD	**Yes**	**No**	**Comments**
Is the variation followed by immediate CD? Reason (only tick the one(s) that apply):	☐		
- change to indication	☐		
- new contra-indication	☐		
- posology change	☐		
- annual flu strain update	☐		
- Active Substance changes for pandemic vaccine	☐		

Committees and Rapporteurs' involvement	**Yes**	**No**	**Comments**
The lead committee for the assessment is:			
CHMP	☐		
PRAC	☐		*In case of stand-alone RMP submission under C.1.11 or non-imposed PASS results without implications for the PI*
CAT	☐		*ATMPs*
PRAC is involved in the CHMP-led (or CAT-led) variation?	☐	☐	*For any procedure where an RMP (update) or a non-interventional PASS without implications for the PI is submitted; otherwise, there has to be a CHMP request for PRAC Advice*
CHMP (or CAT) Co-Rap involvement	☐	☐	*Applicable only to extensions of indication.*

Timetable	**Comments**
Monthly timetable (variation leading to immediate CD or requiring CHMP discussion): ☐ 30-day procedure ☐ 60-day procedure	

Timetable	Comments
Extension of indication /grouped variations ☐ 90-day procedure	*90-day timetable is applicable to extensions of indication and could also apply to grouped variations*
Alternative monthly timetable (variation involving PRAC and not leading to immediate CD or requiring CHMP discussion): ☐ 30-day procedure ☐ 60-day procedure	
Weekly timetable (CHMP-only variation): ☐ 30-day procedure ☐ 60-day procedure	*Weekly timetable is applicable to all procedures except: 90-day procedures, variations involving PRAC or CAT, variations followed by immediate EC Decision, variations requiring CHMP discussion*