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TO: EMEA
Mr. Nicolas Rossignol
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Brussels, December 21, 2007

MSD comments on the Public Consultation on the comitology part of the revision of the Variations Regulations

Dear Mr. Rossignol,

Enclosed are our company's comments on the Public Consultation on the comitology part of the revision of the Variations Regulation, which I am providing you on behalf of Merck Sharp & Dohme (Europe) Inc. MSD (Europe) Inc. is an affiliate of Merck & Co., Inc. (USA).

Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved lives and improved the quality of life for millions of people globally.

The Regulation has been reviewed by MSD's European Regulatory Affairs and Policy experts as well as our in-house legal counsel, who have extensive experience in operating under the current EU Regulatory framework by registering new medicinal products through the European procedures as well as maintaining these marketing authorisations through post-licensing interactions with the EMEA. It was also reviewed by several Regulatory Affairs Managers based in our EU affiliates, who have broad experience from operating under the current EU and various national frameworks for Variations.

MSD strongly supports the Commission's proposal for the revised Variation regulation and broadly agrees with its objectives and suggested concepts as outlined in the consultation paper. However, we would like to suggest that the precise implementation of those concepts may need further improvements to the legal drafting text to ensure that it fully reflects the Commission's strategy paper.

Procedural aspects and timelines need to be matched with the primary objective for a flexible and simple system which allows a faster implementation of scientific progress and important new information for the benefit of patients. We recommend that specific maximum validation timelines are laid down in the Regulation in this respect.

We agree with a default category of Type IB for any unclassified variations and a "safeguard clause" to switch to a Type II variation if the authority can justify in exceptional cases that the evaluation procedure needs to be prolonged based on the adherent risk of the proposed change. A resubmission of documentation and a restart of the evaluation procedure from the beginning should not be required.

We further recommend that the evaluation time for line extensions is shortened in analogy to the Type II variation timeline to allow a simultaneous assessment and approval of new indications, i.e. paediatric indications, in connection with a new strength or dosage form.

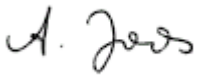
We fully support the extensive options for grouping and worksharing as these concepts will largely contribute to lower numbers of variations. To fully realise the benefits of worksharing, any agreed outcome of the procedure should be transposed into national MAs via a purely administrative step.

Our detailed comments are provided in the attachment.

We are looking forward to the follow-on discussion on the content of the proposed Commission guideline and recommend that adequate time is allocated for a careful reflection and detailed review of the categories, conditions and documentation requirements with all stakeholders. We support the mechanism proposed for easy and speedy updating of this guidance as required by technical and scientific progress.

We welcome the opportunity to comment on this Regulation. Please do not hesitate to contact me should you have any questions.

Yours sincerely,



Angelika Joos

SUBMISSION OF COMMENTS ON BETTER REGULATION OF PHARMACEUTICALS: TOWARDS A SIMPLER, CLEARER AND MORE FLEXIBLE FRAMEWORK ON VARIATIONS

COMMENTS FROM Merck Sharp & Dohme (Europe) Inc.
GENERAL COMMENTS
MSD strongly supports the Commission's proposal for the revised Variation regulation and broadly agrees with its objectives and suggested concepts as outlined in the consultation paper.
Procedural aspects and timelines need to be matched with the primary objective for a flexible and simple system which allows a faster implementation of scientific progress and important new information for the benefit of patients. We recommend that specific maximum validation timelines are laid down in the Regulation in this respect.
The definition and categorisation of variations as laid down in Articles 3 and 4 is very important and should be re-drafted as suggested below.
We welcome the option to seek a scientific recommendation in a variation classification from the Agency according to Article 5. The timeline to deliver such recommendation should be limited to 30 days to avoid unnecessary delay of a variation procedure.
New strengths, pharmaceutical forms and routes of administration requiring an extension procedure can well be evaluated during a timeline similar to a type II variation. We suggest shortening the timeline for the assessment of extension applications to allow speedy patient access.
A work sharing procedure as referred to in Article 24 and coordinated by the Agency is welcomed. However, we recommend that the amendment of any concerned marketing authorisations based on the opinion should be made through an administrative Type IA procedure. Downgrading the variation should not lead into a request for change in the supportive documentation.
We are looking forward to the follow-on discussion on the content of the proposed Commission guideline and recommend that adequate time is allocated for a careful reflection and detailed review of the categories, conditions and documentation requirements with all stakeholders. We support the mechanism proposed for easy and speedy updating of this guidance as required by technical and scientific progress.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Page 3, Article 1	The definition of the scope of the Regulation should also reflect marketing authorisations granted pursuant to Directives 65/65 and	Article 6 of Directive 2001/83/EC , or its equivalent under Directive 65/65/EEC, Article 5 of Directive 2001/82/EC, or its equivalent under

[1] Where available

	81/851.	Directive 81/851/EEC, … Additional definition to be considered: (a) "Approval" means notification of acceptance of a minor or major change provided to the holder by the competent authority at closure of a procedure as a result of the examination of a variation submitted by the holder.
Page 4, Article 3, Definitions 3.-7.	The definition of the variation categories is vital to the Regulation and needs to be clarified. For MRP/DCP products it is logical to use the existing RMS for the variation procedure and for national products when there is no RMS assigned that the holder has the choice. We recommend switching the order. "Approval" should be defined for clarity.	We propose to re-phrase these points as follows: *Article 3 Definitions* 3. A "minor variation of Type I" is a change that has a minimal potential to have a negative effect on the quality, safety or efficacy of the medicinal product concerned. 4. A "major variation of Type II" is a change, which is not an extension and has a substantial potential to have a negative impact on the quality, safety and efficacy of the medicinal product concerned. 5. "Extension" means a change to the medicinal product concerned which requires an amendment to the marketing authorisation from the relevant authority and which fulfils the conditions as listed in Annex I. Delete 6 and 7 8. "Reference Member State" means the Member State as referred to in Article 28 of Directive 2001/83/EC and in Article 32 of Directive 2001/82/EC, or in absence of such, the Member State chosen by the holder with a view to the application of this Regulation. Additional definition to be considered: "Approval" means notification of acceptance of a minor variation or major variation provided to the holder by the competent authority at closure of a procedure as a result of the examination of a variation submitted by the holder.
Article 4	The classifications need to be clarified to highlight that Type I (A immediate, A and B) are only notifications and need no prior approval letters before implementation can take place. The provision for relevant authorities to upgrade unclassified variations to major	*Article 4 Classification of variations* 1. Classification and conditions for minor variations will be set out in detailed guidelines referred to in point (a) of Article 6(1). a) Certain minor variations of Type IA have to be notified to the relevant

	variations based on detailed grounds should be clearly stated.	authority immediately, if they impact the continuous and permanent supervision of the medicinal product concerned. Other minor variations of Type IA have to be notified to the relevant authority within 12 months. They can be implemented prior to or immediately with their notification. b) Minor variations of Type IB have to be notified to the relevant authority and can be implemented if the relevant authority has not requested further information within 30 days. 2. Classification and conditions for major Type II variations, which are not an extension, will be set out in detailed guidelines referred to in point (a) of Article 6(1). Type II variations require approval by the relevant authority before implementation. 3. A variation which is not an extension and whose classification is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) shall be considered a minor variation of Type IB. It can be implemented after 30 days if the relevant authority has neither requested further information nor determined with a detailed justification that the change has a potential negative impact on the quality, safety and efficacy of the medicinal product concerned and requested to change the evaluation to a Type II variation procedure.
Article 5	We fully support the optional provision to request advice on the classification from the EMEA to allow a harmonised interpretation on national variations. The timeframe for this advice needs to be shortened to allow a speedy process.	*Article 5 Scientific recommendations on unforeseen variations* 1. …The Agency shall deliver this recommendation within 30 days following the receipt of the request, taking… 2. The Agency shall publish the recommendations delivered in accordance with paragraph 1, subparagraph 2, after deletion of all information of commercial confidential nature.
Article 6	We recommend including a legal clarification to reflect that the detailed guidelines should ensure that the classifications reflect the level of risk of the proposed change on the medicinal product while promoting administrative simplification.	*Article 6 Guidelines* 1. The Commission, in consultation with the Member States, the Agency and interested parties, shall draw up: a) detailed guidelines on the conditions for classification of variations which are not extensions taking into account their potential impact on quality, safety and efficacy of the medicinal product concerned while promoting administrative simplification.

Article 8	The timeline for acknowledging receipt and validating the application should be shortened. This timeline reflects current business practice. In general, validation timelines should be included in the legal text.	*Article 8 "Do and Tell" procedure with Type I A variations (National)* 2. Within 14 calendar days following receipt of a notification referred to in paragraph 1, the relevant authority shall close the procedure in accordance with Article 21(1)
Article 9	We recommend clarifying the legal text for the evaluation of Type IB variations, the required documents and the possible switch mechanism to Type II. Maximum validation timelines have been added. For unclassified variations, a detailed justification should be provided which would be used instead of the amended expert statement, if the Type IB is switched to Type II based on an authority request. A re-submission should not be necessary. The timetable would only be amended to reflect the further Type II procedure. Articles 9 and 10 have been amended accordingly. A clarification has been included to prevent changing the classification if it has previously been determined by the EMEA according to Article 5.	*Article 9 "Tell, Wait and Do" procedure for Type IB variations (National)* 1. … 2. The holder shall submit simultaneously to all relevant authorities a notification including the relevant elements listed in paragraph 2 of Annex III. If the notification fulfils the requirements laid down in the first subparagraph, the relevant authority shall acknowledge receipt of a valid notification within 14 calendar days. 3. If within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 2 subparagraph 2… 4. Within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 2 subparagraph 2 and where the relevant authority is of the opinion that the notification cannot be accepted, it shall inform the holder … 5. By the way of derogation from the second and third subparagraphs of paragraph 4, where the classification of the variation concerned is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) and a scientific recommendation on the classification by the Agency has not been given according to Article 5, and the relevant authority is of the opinion that the ~~referred~~ variation has a substantial potential to have a negative impact on the quality, safety and efficacy of the medicinal product concerned, the variation shall be evaluated in accordance with the procedure laid down in paragraphs 3 to 5 of Article 10. 6. …
Article 10	Maximum validation timelines have been added. Evaluation periods for safety related changes and AEs are suggested to be shortened and fixed as 30 days to allow the speedy update of	*Article 10 "Prior Approval" procedure for Type II variations (National)* 1. …

	product information for the benefit of patients. We recommend fixing the maximum timeline for the assessment of the supplementary information provided by the holder to avoid any delays or unpredictability in timelines.	2. … If the application fulfils the requirements laid down in the first subparagraph, the relevant authority shall acknowledge receipt of a valid notification within 14 calendar days. 3. The relevant authority shall evaluate the valid application referred to in paragraph 2 within 60 days following its receipt. By way of derogation from the first subparagraph: (a) the relevant authority may reduce the period referred to in that subparagraph, having regard to the urgency of the matter. (b) The period referred to in that subparagraph shall be 30 days if the change is related to adverse experience, new safety information or as a consequence of Article 9 (5). (c) The period referred to in that subparagraph shall be 90 days if the variation is concerning a change or addition of a therapeutic indication or a non-food producing target species. 4. Within the period laid down in paragraph 3, the relevant authority may request the holder to provide supplementary information within a time limit set by that competent authority. The procedure shall be suspended until such supplementary information has been provided. The relevant authority shall take the supplementary information into account within 30 days of its receipt. ~~In this case the period laid down in paragraph 3 may be extended for a further period to be determined by the relevant authority.~~ 5. …
Article 12	Please add DCP. The timeline for acknowledging receipt and validating the application should be shortened. This timeline reflects current business practice.	*Article 12 "Do and Tell" procedure for Type IA variations (MRP/DCP)* 2. Within 14 calendar days following receipt of a notification referred to in paragraph 1, the relevant authority shall close the procedure in accordance with Article 21(2)
Article 13	Please add DCP. We recommend clarifying the legal text for the evaluation of Type IB variations, the required documents and the possible switch mechanism to Type II. Maximum validation timelines have been added.	*Article 13 "Tell, Wait and Do" procedure for Type IB variations (MRP/DCP)* 1. … 2. The holder shall submit simultaneously to all relevant authorities a notification including the relevant elements listed in paragraph 2 of

	For unclassified variations, a detailed justification should be provided which would be used instead of the amended expert statement, if the Type IB is switched to Type II based on an authority request. A re-submission should not be necessary. The timetable would only be amended to reflect the further Type II procedure. Articles 9 and 10 have been amended accordingly. A clarification has been included to prevent changing the classification if it has previously been determined by the EMEA according to Article 5.	Annex III. If the notification fulfils the requirements laid down in the first subparagraph, the competent authority of the reference Member State shall acknowledge receipt of a valid notification and start the procedure <u>within 14 calendar days.</u> 3. If within 30 days following the acknowledgement of receipt of a valid notification referred to in <u>paragraph 2 subparagraph 2</u>… 4. <u>Within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 2 subparagraph 2</u> and where the competent authority of the reference Member State is of the opinion that the notification cannot be accepted, it shall inform the holder … 5. By the way of derogation from the second and third subparagraphs of paragraph 4, where the classification of the variation concerned is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) <u>and a scientific recommendation on the classification by the Agency has not been given according to Article 5</u>, and the competent authority of the reference Member State is of the opinion that the ~~referred~~ variation has a substantial potential to have a negative impact on the quality, safety and efficacy of the medicinal product concerned, the variation shall be evaluated in accordance with the procedure laid down in paragraphs <u>3</u> to 6 of Article 14. 6. …
Article 14	Please add DCP Maximum validation timelines have been added. Evaluation periods for safety related changes and AEs are suggested to be shortened and fixed as 30 days to allow the speedy update of product information for the benefit of patients. We recommend fixing the maximum timeline for the assessment of the supplementary information provided by the holder to avoid any delays or unpredictability in timelines.	*Article 14 "Prior Approval" procedure for Type II variations (MRP/<u>DCP</u>)* 1. … 2. … If the application fulfils the requirements laid down in the first subparagraph, the competent authority of the reference Member State shall acknowledge receipt of a valid notification <u>and start the procedure within 14 calendar days</u> and inform the other relevant authorities of the date of the start of the procedure laid down in paragraphs 3 to 6. 3. Within 60 days from the date referred to in paragraph 2 second

		subparagraph, the competent authority of the reference Member State shall prepare an assessment report and a draft decision on the application, which shall be addressed to the other relevant authorities. By way of derogation from the first subparagraph: (a) the competent authority of the reference Member State may reduce the period referred to in that subparagraph, having regard to the urgency of the matter. (b) The period referred to in that subparagraph shall be 30 days if the change is related to adverse experience, new safety information or as a consequence of Article 13 (5). (c) The period referred to in that subparagraph shall be 90 days if the variation is concerning a change or addition of a therapeutic indication or a non-food producing target species. 4. …In this case: (a) the competent authority of the reference Member State shall inform the other competent authorities concerned of its request for supplementary information: (b) the procedure shall be suspended until such supplementary information has been provided: (c) the competent authority of the reference Member State shall take the supplementary information into account within 30 days of its receipt. ~~The period laid down in paragraph 3 may be extended for a further period to be determined by the competent authority of the reference Member State.~~
Article 16	This Article has been amended to clarify and reflect the current provisions of the coordination group as laid down in Directive 2001/83/EC. However, this phase should only take 30 days to reach an agreement on a variation. This is justified by the shorter timeline of the variation process and the less complex issues. A referral to CHMP is always possible as a further conciliation step.	*Article 16 Coordination group and arbitration (MRP/DCP)* 1. … Within the coordination group, all Member States shall use their best endeavour to reach agreement on the action to be taken. They shall allow the applicant to make his view known orally or in writing. If, within 30 days of the communication of the points of disagreement, the Member States reach an agreement, the reference Member State shall record the agreement and close the procedure according to Article 21(2).

		2. The procedure referred to in Article 35(2) of Directive 2001/83/EC and Article 39 (2) or Directive 2001/82/EC shall apply in the following cases: (a)… (b)… (c)… (d) If the Member States fail to reach an agreement within the 30-day period laid down in paragraph 1.
Article 17	The timeline for acknowledging receipt and validating the application should be shortened. This timeline reflects current business practice.	*Article 17 "Do and Tell" procedure for Type IA variations (CP)* 2. Within 14 calendar days following receipt of a notification referred to in paragraph 1, the Agency shall close the procedure in accordance with Article 21(3)
Article 18	Please see our comments on Articles 9 and 13. The validation by EMEA is currently performed within 5 working days. We further suggest that the competent scientific Committee (CHMP or CVMP) of the EMEA should take the decision to request further information in stead of the Commission as they are responsible for the evaluation of the scientific data which is a basis for determining the impact of the change.	*Article 18 "Tell, Wait and Do" procedure for Type IB variations (CP)* 1. … 2. The holder shall submit to the Agency a notification including the relevant elements listed in paragraph 2 of Annex III. If the notification fulfils the requirements laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid notification and start the procedure within 7 calendar days. 3. If within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 2 subparagraph 2… 4. Within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 2 subparagraph 2 and where the competent Committee of the Agency is of the opinion that the notification cannot be accepted, it shall inform the holder … 5. By the way of derogation from the second and third subparagraphs of paragraph 4, where the classification of the variation concerned is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) and a scientific recommendation on the classification has not been given according to Article 5, and the competent Committee of the Agency ~~or the Commission~~ is of the opinion that the ~~referred~~ variation has a substantial potential to have a negative

		impact on the quality, safety and efficacy of the medicinal product concerned, the variation shall be evaluated in accordance with the procedure laid down in paragraphs 3 to 5 of Article 19. For variations submitted under Article 24, the variation shall be evaluated in accordance with the procedure laid down in paragraphs 3 to 4 of Article 19. 6. …
	Please see our comments on Articles 10 and 14. We further suggest including the "competent Committee" of the Agency in the scientific evaluation.	*Article 19 "Prior Approval" procedure for Type II variations (CP)* 1. … 2. … If the application fulfils the requirements laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid notification and start the procedure within 14 calendar days. 3. The competent Committee of the Agency shall issue and opinion on the valid application referred to in paragraph 2 within 60 days following its receipt. By way of derogation from the first subparagraph: (a) the competent Committee of the Agency may reduce the period referred to in that subparagraph, having regard to the urgency of the matter. (b) The period referred to in that subparagraph shall be 30 days if the change is related to adverse events, new safety information or as a consequence of Article 18 (5). (c) The period referred to in that subparagraph shall be 90 days if the variation is concerning a change or addition of a therapeutic indication or a non-food producing target species. 4. Within the period laid down in paragraph 3, the competent Committee of the Agency may send the holder a request for supplementary information within a certain time limit set by that Committee. The procedure shall be suspended until such supplementary information has been provided. The competent Committee of the Agency shall take the supplementary information into account within 30 days of its receipt. ~~In this case the period laid down in paragraph 3 may be extended for a further period to be~~

		~~determined by the Agency.~~ 5. …
	We fully support the principle set forth in the Article 22 that minor (Type I) and major (Type II) changes can be implemented prior to amending the marketing authorisation and welcome the legal provisions to this respect. We agree that an amendment to the Marketing authorisation can be done via a "sweep" mechanism every 6 months. However for major type II variations which mostly involve change to the product information, we suggest that MA decisions are updated within one month to allow the timely availability of amended product information in EudraPharm. In case a Commission Decision is needed, this should occur within 45 days as it is current business practice.	*Article 21 Closure of procedures* 1. … (b) Where necessary, the relevant authority shall amend the marketing authorisation in accordance with the accepted variation or notification - within <u>one month</u> after sending the information referred to in point (a) in the case <u>of major variations;</u> - within six months after sending the information referred to in point (a) in the other cases 2. … (b) Without prejudice to Article 16, each relevant authority shall, were necessary, amend the marketing authorisation in accordance with the accepted variation or notification - within <u>one month</u> after sending the information referred to in point (a) in the case <u>of major variations;</u> - within six months after sending the information referred to in point (a) in the other cases. 3. … (b) the Commission shall, where necessary and based on <u>an opinion by the competent Committee of</u> the Agency, amend the marketing authorisation <u>pursuant to Articles 10 and 32 of Regulation 726/2004 and</u> update the Community Register of Medicinal Products provided for in Articles 13(1) and 38 (1) of Regulation 726/2004 accordingly. (c) The amendment to the marketing authorisation referred to in point (b) shall be made: - within <u>45 days</u> following receipt of the information referred to in point (a) in the case <u>of major variations</u>; - within six months following receipt of the information referred to in point (a) in the other cases. 4. …
	The assessment time needed for the new clinical data presented for a	*Article 23 Extensions*

	new therapeutic indication seems to be equivalent to any new quality data provided for a new strength. New indications, e.g. paediatric indications, are often related to lower tablet strengths or new formulations and we strongly recommend that these can be assessed within the variation timelines to allow a speedy access for patients.	An application for an extension of a marketing authorisation shall be evaluated in accordance with the same procedure as laid down in Articles 10 (3), 14(3) or 19 (3) ~~as for granting of the marketing authorisation to which it relates.~~
	We fully support the principle of work sharing and the proposal to involve the EMEA Network structure in this assessment. However, to make such optional procedure interesting for users, a general downgrading to Type IA for the national implementation is required. Otherwise these two steps will only unnecessarily prolong timelines without real justified benefit as there is always a risk that the discussion in the second step is re-opened. We have clarified the procedure to align it with the procedures for other types of authorisations and added clear validation timelines. The second step defining the national implementation in the local marketing authorisation has been added as paragraph 8.	*Article 24 Work sharing* 1. … 2. The holder shall submit to the Agency an application accompanied by the elements listed in points (a) to (g) (1) of paragraph 2 of Annex III. In the application referred to in the first subparagraph, the holder shall specify: (a) whether the concerned marketing authorisations all relate to the same medicinal product; or (b) whether the concerned marketing authorisations relate to different medicinal products. If the application fulfils the requirements laid down in the first and second subparagraphs, the Agency shall acknowledge receipt of a valid application within 14 calendar days. 3. For minor Type IB variations the evaluation is following the procedure as laid down in Article 18, paragraphs 3 to 5. 4. For major Type II variations the evaluation is following the procedure as laid down in Article 19, paragraphs 3 to 4. 5. For extensions the evaluation is following the procedure as laid down in Article 23. 6. Where it reaches a final opinion on the application as referred to in The Agency shall sent it to the holder and to all relevant authorities, together with a list of all the marketing authorisations concerned. 7. Upon request from the Agency, concerned Member States shall

		provide any information related to the marketing authorisations affected by the variations, which is deemed relevant for the Agency for the purpose of: - verifying the validity of the application referred to in paragraph 2; - issuing the final opinion referred to in paragraph 6. 8. The relevant authorities shall amend the concerned marketing authorisations according to Article 8(2) or Article 12 (2).
	Please amend Article 26 to reflect the current business practice. A timeline for implementation of an urgent safety restriction should be agreed between the holder and the relevant authorities.	*Article 26 Urgent Safety Restriction* 1. … 2. The holder shall take urgent safety restrictions where requested by a relevant authority. 3. The urgent safety restriction referred to in paragraphs 1 or 2 shall be implemented within a timeframe, as agreed with the relevant authorities. 4. The corresponding variation application reflecting the urgent safety restriction shall be submitted immediately and in any case no later than 15 calendar days after the initiation of the urgent safety restriction.
	Please add a heading to Annex II	*ANNEX II Requirements for Grouping of Variations*
	Please add a heading to Annex III Please clarify that replacement pages for regulatory dossiers are required. For Type IB variations, we suggest including a detailed justification of the change which could serve as the revised expert statement if the variation is switched to a Type II procedure.	*ANNEX III Regulatory Submission Documents* 1. … (c) …That description shall include all necessary documents demonstrating that the conditions laid down in the detailed guidelines referred to in point (a) of Article 6(1) for the referred variation(s) are met, including amendments to the regulatory documents. 2. … (e) in case of - minor variations Type IB according to Articles 9 (5), 13(5) or 18 (5), a detailed justification - major variations of Type II and extensions, an addendum to or update of the existing expert reports/overviews/summaries

		to take account of the variations applied for. 3. …

Please feel free to add more rows if needed.