February 2015

Variations in eCTD format
Q&A document

This document uses a question and answer format to give some guidance when submitting variation applications in eCTD format.

For general guidance on variations, please refer to the CMDh website (variation procedures). Further guidance on the eCTD format can be found at the EMA eSubmission website.

1. GENERAL POINTS FOR ALL VARIATIONS

Q 1.1a: Should the submission mode element in the envelope be used for sequences associated with variations and extensions?

A1.1a: Yes, this is specified in the EU Module 1 Specification, and in the general terms in the EU Procedural Guideline.
The submission mode has to be used, and must have an identical value for all sequences concerning a certain extension or variation regulatory activity.
The submission mode should only be used for sequences that concern an extension or variation.

Q 1.1.b: What submission type value should be used for a so called grouping with a mix of different types of variation?

A1.1.b: For groupings, the submission type value should be the “highest” variation or extension type. For example, a group consisting of a Type IA and a Type IB variation should use the submission type value “var-type1b”; a group consisting of a Type II variation and an extension should use the submission type value “extension”.

Q 1.2: Is the high level submission number element used only for the following instances?

1. **Groupings and**
2. **Worksharing procedures**

A 1.2: Yes, this is specified in the EU Module 1 specification and it is used in Groupings and Worksharing procedures concerning several MAs (products), when separate eCTD sequences have to be submitted for each MA (product) and each of these sequences should have an identical submission number. This submission number always has an "xxxx" string inside because several MAs (products) are concerned.

Q 1.3: Is the eCTD submission mode applicable to all sequences concerning a particular variation activity (i.e. not just the initial variation application but also all subsequent sequences concerning that variation including any validation sequences, responses to questions, closing sequences etc.)?

A 1.3: Yes, this element must be populated for **ALL** sequences which will be submitted for the particular variation or extension concerned. (See diagrams in A 2.1)

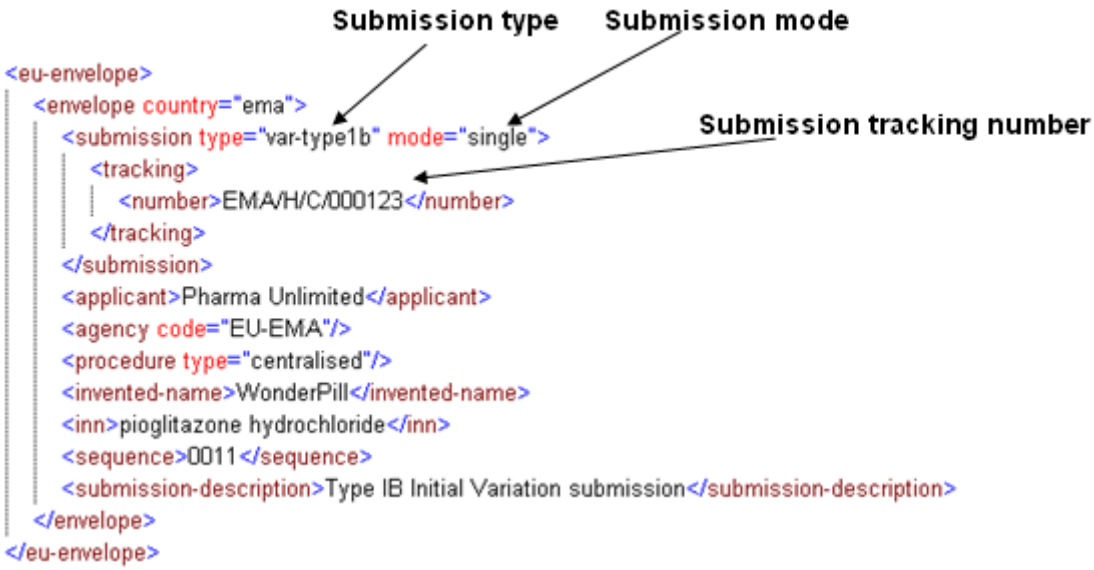
Note that in the rare occasion of one sequence (a response submission) covering multiple regulatory activities, of which at least one is a grouped variation, the submission mode "grouping" must be used even though some of the variations are single variations.

2. SINGLE VARIATION FOR A SINGLE MA

Q 2.1: How should a single variation be presented?

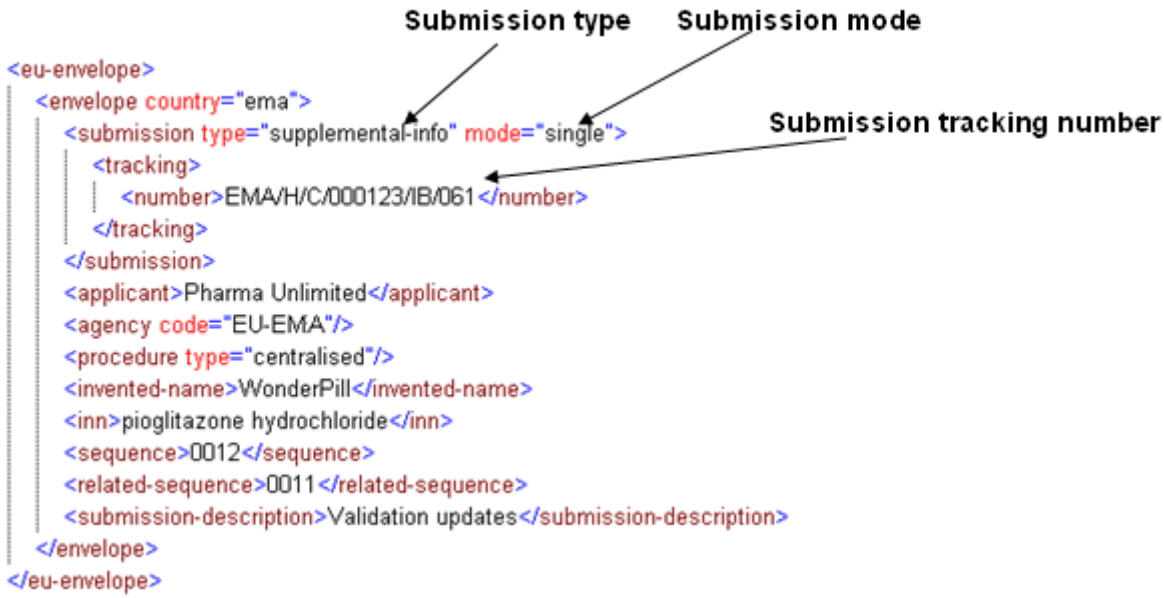
A 2.1: The diagram below shows the envelope element from the eu-regional.xml file for a single variation for a single MA. The use of the submission type, submission mode and submission tracking number has been highlighted. This example is for a Centralised Procedure submission and shows the first sequence in the variation activity.

Submission type = the type of the variation (e.g. "var-type1b")
Submission mode = "single"
Submission tracking number = For first sequence in the regulatory activity, use just the procedure root number (e.g. "EMEA/H/C/000123")



This diagram shows an example of the element values that might be used in a subsequent sequence in the activity.

Submission type = “supplemental-info” (or “corrigendum”)
Submission mode = “single”
Submission tracking number = The full variation number should be used (e.g. “EMEA/H/C/000123/IB/061”)



Tracking number for MRP products: see CMDh BPG for submission and processing of Variations in MRP, Chapter 1 (e.g. DE/H/0450/001/IA/001)

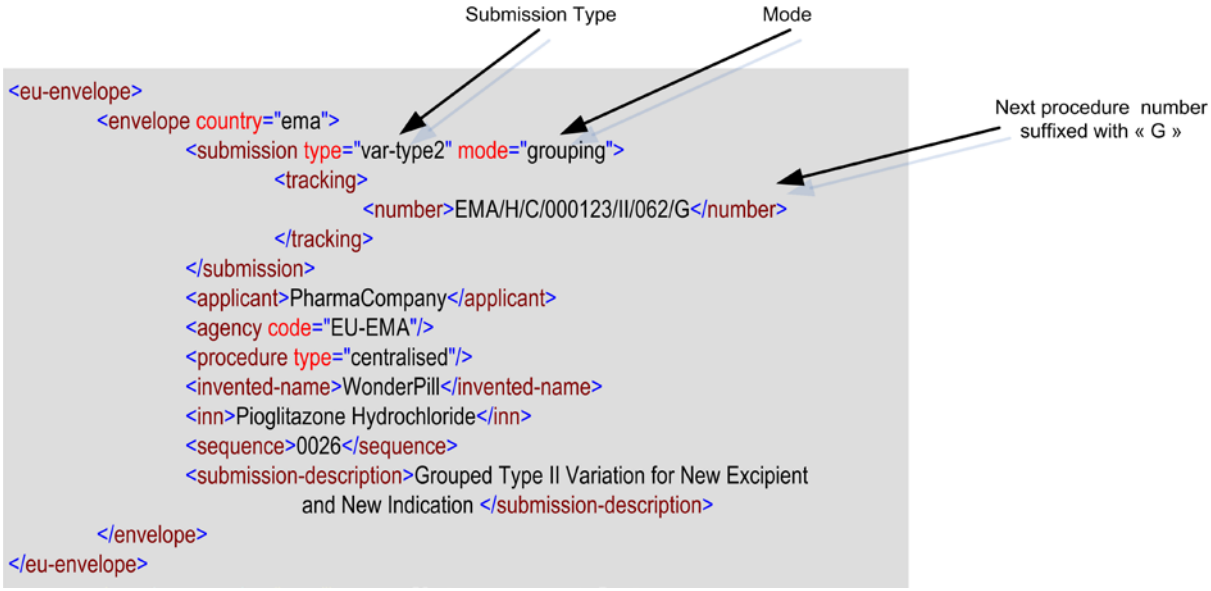
3. GROUPED VARIATIONS FOR A SINGLE MA

This category includes grouped variations, or a grouping of Type IA variations for only a single MA.

Q 3.1: How should a grouped variation of the same type, for a single MA, be presented?

A 3.1: The diagram below shows an *example* of a Centralised Procedure variation grouping two Type II variations for the same MA.

Submission type = the identical type for all variations (e.g. “var-type2”)
Submission mode = “grouping”
Submissions tracking number = use the next procedure number but suffixed with ‘G’ (e.g. “EMEA/H/C/000123/II/062/G”)



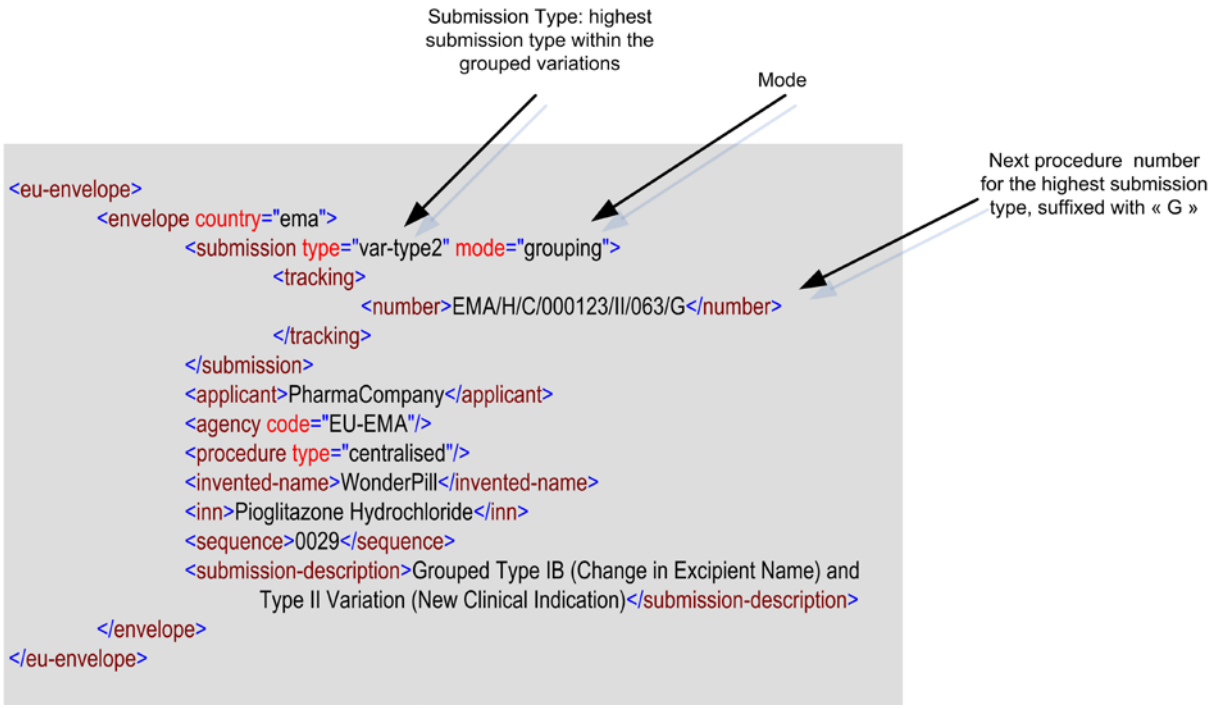
Tracking number for MRP products: see CMDh BPG for submission and processing of Variations in MRP, Chapter 1 (e.g. AT/H/0234/II/003/G).

Q 3.2: How should a grouped variation of different types, for a single MA, be presented?

A 3.2: The diagram below shows an *example* for a Centralised Procedure variation for a grouping of a Type IB and a Type II variation for the same MA.

Submission type = the highest submission type within the grouped variations (e.g. if grouped variations are IB and type II, use “var-type2”)
Submission mode = “grouping”

Submission tracking number = use the next procedure number for the highest submission type with the suffix “G” (e.g. “EMEA/H/C/000123/II/063/G”)



Tracking number for MRP products: see CMDh BPG for submission and processing of Variations in MRP, Chapter 1.

Q 3.3: How should the single individual sequences included in a grouped variation be created?

A 3.3: Submissions of grouped variations for a single MA should be submitted as a single eCTD sequence for the product concerned. The cover letter and Application Form should identify the individual variations included in the grouping.

Q 3.4: How should the applicant differentiate the content of the different variations included in the grouping?

A 3.4: This should be done within the application form and cover letter, rather than in the files submitted in the submission. The supportive documentation would be integrated.
For worksharing procedures, there is the need to include also which products are relevant to which CMSs. Every included product has to have its own eCTD sequence.

Q 3.5: Should the Applicant submit a "Consolidation Sequence" if there are rejected variations?

A 3.5: Rejected variations should not appear in the current view. It is understood that a single decision will be made about a grouping but that this could include separate approval and rejections of each individual variation. In the case of rejected variations, the applicant should submit a "consolidation" sequence to remove from the current view of the eCTD any documents associated with the rejected variation. This should be created in the following manner:

1. Any leafs associated only with the rejected variation, and where content was submitted for the first time in this section, should be updated with a "delete" operation leaf
2. Any leafs associated only with the rejected variation, and where content was submitted for a second or subsequent time in this section (i.e. the leaf for the variation in question was submitted with a "replace" operation"), should be updated with a "replace" operation leaf that points the content back to the version of the leaf used prior to the submission of the variation that has been rejected.
3. Any leafs associated with the rejected variation but with content also shared with other approved variations should be updated with a "replace" operation leaf that points to a new content file that contains only the approved content (i.e. the proposed texts associated with rejected variation have been reverted back to the text that was approved before the start of the grouped variation activity).

When creating the consolidated sequence, it is important to note that the content to be removed from the "current view" may be contained in more than one sequence (e.g. if a Type II variation is rejected, the content may be in the original sequence for the variation application, a sequence for the validation updates, in a sequence for responses to questions, etc.). The applicant should submit only one single consolidation sequence that removes the content associated with the rejection from all of the previously submitted sequences associated with the variation activity. Within the envelope, the "submission type" should be identified as supplemental-info. The consolidation sequence is part of the variation activity, so it should have a "related-sequence" value that matches the sequence number of the initial sequence for the variation activity. Ideally, the "submission-description" should include some text to identify the sequence as a consolidation sequence after variation rejection.

For complete rejections of a variation: the current view should only show the latest approved document versions and possibly pending documents from ongoing new variations and a "consolidated sequence" should be submitted as described above.

Q 3.6: Should the applicant submit a "consolidation sequence" when a variation within a grouping is withdrawn?

A 3.6: In the case of withdrawn single variations from a grouping during an ongoing assessment of a grouped variation, the applicant should submit a "consolidation"

sequence to remove from the current view of the eCTD any documents associated with the withdrawn variation. This should be created as described in A 3.5.

Note that the "submission type" to be identified in the envelope should be supplemental-info. The submission type value of withdrawal should not be used in this circumstance and should be reserved for an activity to withdraw a license/product. Ideally the "submission-description" should include some text to identify the sequence as a consolidation sequence after withdrawal of a variation.

Q 3.7: What shall I do if during the assessment of a grouped variation including different types of variations for a single marketing authorisation, the highest variation(s) that are used to qualify the group submissions are withdrawn?

A 3.7: The Procedure number will not change. There are no other consequences for eCTD than identified above under rejection/withdrawal (see A 3.5 and A 3.6).

Q 3.8: Withdrawing – Rejecting for all submission modes
What should I do if the complete variation is rejected?
What should I do if the complete variation is withdrawn?

A 3.8: If a complete variation is withdrawn or rejected, the applicant should submit a consolidation sequence to remove the scientific and regulatory content from the current view of the eCTD submission in the lifecycle. The general rules described in A 3.5 and A 3.6 should be followed.

However, not all of the content submitted in the rejected or withdrawn submission should be removed from the current view of the eCTD. It is useful to retain certain administrative information in the current view and some scientific or regulatory information may be used in future submissions (e.g. a clinical study report for a rejected new indication will still contribute data about clinical safety in future submissions). Therefore, the following rules should be applied

In Module 1: The original cover letter and application form should not be removed from the current view. The tracking table should also not be removed. All other documents should be removed following the rules described in A 3.5. Particular care should be taken to remove from the current view the versions of any labelling documents associated with the rejected or withdrawn variation.

In Module 2: All summary documents should be removed from the current view.

In Module 3: All content files associated with the rejected or withdrawn variation should be removed from the current view so that only the previously approved/submitted content remains in the current view.

In Modules 4 and 5: The applicant should not remove from the current view any content unless the reviewing agency specifically requests to remove it.

4. TYPE IA GROUPING AND WORKSHARING COVERING SEVERAL MAS

This category includes grouped type IA variations for several MAs and worksharing procedures.

Q 4.1: How should the single individual sequence for each of the eCTDs covered by a grouping or a worksharing procedure be created?

A 4.1: When creating the single sequence for a grouped or worksharing variation across several MAs, the applicant should note that the current eCTD specification cannot manage more than one MA (product) in a single eCTD sequence. Therefore, the general process will be to create a separate eCTD sequence for each eCTD lifecycle. This will allow the content and envelope information associated with each product to be managed, as well as allowing the applicant to preserve the lifecycle leaf information. In general the points in Q 3.6 apply.
A new eCTD sequence, containing the relevant documents, for each product concerned by the worksharing procedure should be submitted. I.e. submit the individual eCTD for each product as is normally the case, but provide these as part of one application even if each dossier needs to be updated individually (lifecycle maintenance). Worksharing will then subject these eCTD submissions to a common evaluation procedure, but the normal eCTD submission principles continue to apply.

In addition, the applicant should pay attention to the following points when creating the individual eCTD sequences for each MA (product):

1. Within each MA (product) specific sequence the applicant should edit the envelope values to reflect the product specific values. – In particular, attention should be paid to the following envelope metadata values which will almost certainly be different for each product
    a. submission tracking number – this should reflect the product specific procedure and tracking numbers
    b. INN and invented name – this should reflect the product specific INN and invented names
    c. sequence and related-sequence – this should reflect the product specific sequence number and related sequence

    Note: The following envelope metadata values should be identical for all products

d. High Level submission number – this is the Grouping or Worksharing procedure number and is the key identification number used to associate all of the separately submitted sequences
e. submission type and mode – these must be identical for each MA (product) specific eCTD sequence being made for the grouped/worksharing submission
f. agency code – the authority identified must be identical for all products.

Note: The following envelope metadata values may be the same or different for any/all MAs (products)

g. applicant
h. procedure type
i. submission description

For further information on how to populate the EU Module 1 Envelope, consult the EU M1 specification.

2. Content for the submission should be identical in each sequence for each MA (product) for the following sections of the CTD.
    a. Cover letter
    b. Application form
    c. Content associated directly with the proposed change

    Where the content is identical the applicant should try to use the same leaf titles in each product specific sequence.
    While the content of these sections may be identical, it should be noted that the leaf lifecycle information will almost certainly not be the same from one MA (product) specific sequence to the next in the Grouping or Worksharing application. For example, a variation to introduce a new analytical method may be "new" for one product but a "replace" leaf for another product. It is recommended to give information in the cover letter about any common documents in the different eCTDs.

3. Content for the submission may be different for each sequence for each MA (product) in other parts of the CTD dossier structure, particularly for the product specific supporting documentation for a variation (e.g. the information on specific batches of a product used to show that a new analytical method is valid, or the product specific SmPCs submitted when the MAH address changes).
    It should be noted that each MA (product) specific sequence must only contain content for that particular MA, so any content specific to another MA should not be included in that particular sequence. Inclusion of content for another MA may confuse the assessor and may lead to delays while the issues are resolved.

It is expected that for each product, there should be a separate eCTD sequence submitted, each with its own envelope. The submission will contain a common application form and common cover letter.

Q 4.2: In cases where we have created several eCTD sequences (with the same content but different envelopes for different products), how should the variation be sent to the Authorities (one submission with all sequences vs. one submission per sequence)?

A 4.2: Ideally one submission (CESP, Eudralink, CD/DVD) containing all eCTD sequences for all products concerned in a worksharing procedure or grouped variation covering multiple MAs should be submitted, but in separate folders.
For submissions to EMA via eSubmission Gateway, a separate submission has to be made for each eCTD sequence (multiple eCTD sequences cannot be submitted as part of one transmission via gateway). EMA does not accept submissions for CP on CD/DVD.

Q 4.3: What shall the Applicant do if at the start of a "grouped Type IA" or "worksharing" procedure covering more than one MA the number is not assigned yet?

A 4.3: This is specified in the EU Module 1 specification: it should be indicated in the envelope as "to be advised". This will for instance apply to CP submissions, as the procedure number is only allocated by EMA at time of receipt of the application.
In case of MRP – the number should always be assigned by the RMS in advance and indicated in the envelope.

Q 4.4: How should the grouping of type IA variation(s) for multiple MAs be presented?

A 4.4: A separate eCTD sequence must be prepared for each product. (see Q 4.1)

Q 4.5: How should a worksharing procedure (type IB and / or Type II variations and/or grouped variations) for multiple MAs be presented?

A 4.5: A separate eCTD sequence should be submitted for each product with a separate envelope for each product. (see Q 4.1)

5. WORKSHARING APPLICATION ISSUES

Q 5.1: How should an MAH submit a worksharing application for multiple products for which the dossiers are in different format (e.g. eCTD, NeeS, paper). How can the applicant ensure that the worksharing application is presented and received as a 'complete' application?

A 5.1: The data should be received for each product individually, i.e. as eCTD, NeeS or paper, as applicable. This will allow the lifecycle for eCTD submissions to be maintained and other formats to be used as needed. The fact that one of the products is in eCTD does not make it mandatory to submit the variation for the other non-eCTD products also in eCTD. Each product can continue its previous format. However, there will be only one evaluation procedure. The cover letter should very clearly state what is being submitted and in which format.
Variations can be submitted in eCTD format, even if the previous dossier was in paper or NeeS (i.e. a format change is recommended at the start of a new regulatory activity, e.g. a variation). Refer to the EU Harmonised Technical Guidance for eCTD.
NeeS and eCTD submissions should preferably be sent in one single CESP/Eudralink delivery or be presented on the same hard medium (CD/DVD). Also see A 4.2.

Q 5.2: Worksharing - How should an MAH submit a worksharing application for multiple products which may have different CMSs? Is there any difference if a particular MS or the EMA acts as reference authority?

A 5.2: The reference authority, whether it is an RMS or handled through EMA, will need to receive all applications, even if some products are not authorised in that country, as the reference authority needs to have all of the variations to do the full assessment.
Each CMS should in principle only receive the applications for the products which are relevant to them (e.g. where the NCA is CMS and only one of the variations in the worksharing procedure is marketed in that country, they only need to receive the information for that specific product). However, for electronic submissions, the same CESP/Eudralink delivery or CD/DVD containing all products can be submitted to all CMSs/MSs and the eCTD envelope metadata be used to identify the products relevant in each CMS/MS.

Where EMA acts as reference authority the same application should be submitted to all National Competent Authorities involved (RMS(s) and CMS(s)), even if some products are not relevant to some MS(s).

6. OTHER ISSUES

Q 6.1: Where to put the details about an Article 5 procedure in the dossier?

A 6.1: The Art 5 application itself should not be included in the eCTD lifecycle as it is a preparatory submission, in advance of the real variation submission eCTD. It is comparable to a scientific advice or pre-submission meeting. Where relevant, a reference to the Article 5 recommendation as published on the EMA or CMD website should be given in the variation application form.

Q 6.2: How to handle an upgrade of a type IB to a type II at validation.

A 6.2: The Type IB application would not be invalided as such, but would be upgraded to a Type II.
A new eCTD sequence with a new sequence number needs to be submitted including a new application form and correct envelope data.

Useful links:

eSubmission website: *http://esubmission.ema.europa.eu/index.htm*
CAP Dossier Requirements:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500003980.pdf
CMDh eSubmission website: *http://www.hma.eu/277.html*
CMDh procedural guidance for variations: *http://www.hma.eu/96.html*

Change Record:

Version	Timeline	Authors
Up to version 5	January 2015	CMDh, EMA, TIGes
Version 6	February 2015	eSubmission CMB – Human Harmonisation Group members