

**AD-HOC WORKING GROUP ON
VALIDATION ISSUES/NATIONAL REQUIREMENTS
POSITION PAPER COMMON GROUNDS SEEN FOR INVALIDATION/
DELAYING DAY 0**

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CMD(h) has set up a *Working Group on Validation issues/National requirements in MR/DC procedures* in order to achieve transparency about raised invalidation/delayed validation issues and consequently avoid procedural delays. The working group has defined the most common grounds for invalidation/delayed validation for variations¹ and applicants are encouraged to be more thorough when compiling the documentation before submission of the application.

- The application form is either incorrect and/or incomplete with necessary information missing:
For example:
 - Incorrect procedure number².
 - Incorrect or missing CMSs.
 - An original signature is absent.
 - The name of the medicinal product is not the name approved.
 - The MA number(s) is incorrect.
 - More than one product/strength are included in the same application form.
 - Present/proposed is not filled in or incomplete.
 - Boxes about amended product information are not ticked off correctly (when applicable).
 - Incorrect change code specified.
 - Type IB and II variation is incorrectly specified (e.g. in case of variation application concerning quality part “Other” has been marked instead of “Quality”).
 - Justification with reference to annex III for grouping of type IB and II variations according to art. 7(2b) is missing.
 - The single variation box is ticked although the application concerns a grouping of variations or the grouping box is ticked although the application concerns a single variation.
 - The change is applied as a Type IB unforeseen variation although the change is classified in the classification guideline.
 - Misinterpretation of foreseen Type IB versus unforeseen Type IB.
 - Grouped variation: Boxes indicating which types of variations are included in the grouping have not all been ticked.

¹ Guidance on dossier requirements are given in

- *Commission Regulation (EC) No 1234/2008 of 24 November 2008~~1084/2003 of 3 June 2003~~:*
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2003_1084/reg_2003_1084_en.pdf
http://ec.europa.eu/health/files/eudralex/vol-1/reg_2008_1234/reg_2008_1234_en.pdf
- *Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (February 2010):*
http://ec.europa.eu/health/files/eudralex/vol-2/c17_1/c17_1_en.pdf
- *Guideline on dossier requirements for type IA and type IB notifications (July 2006):*
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/e/var_type_1a1b_guideline_06_2006.pdf

² For example MRP variation number incorrect (e.g. XX/H/0100/001-002/IA/01),
Specific number for each strength/pharmaceutical form should be stated (e.g. XX/H/0100/001/IA/01 and XX/H/0100/002/IA/01).

- For Type IA notifications: Implementation date is missing.
 - Grouped variation: It is unclear which variation numbers from the classification guideline are included in the grouping, especially if the same variation number is applied more than once.
 - Grouped variation: Precise scope has not been specified for all variations included in the grouping.
- **Ce**checklist:
- ~~according to the regulation is missing (for type IA or IB applications)~~
 - ~~The form is only partially completed, with necessary information missing.~~
 - Copy of the relevant page(s) from the Guideline for the change(s) applied with the relevant boxes for conditions (Type IA) and documentation (both for Type IA and where specified Type IB) ticked is either missing or not appropriately completed.
 - Grouped variation: Completed checklist has not been provided for each individual Type IA and Type IB variation included in the grouping.
- The grouped application regards a mix of products authorised through national procedure and MRP/DCP.
 - Grouped variation: Some changes do not apply to all the MAs included in the grouping.
 - Missing or incorrect fee.
 - The application has not been submitted in all MS even though this has been declared in the dispatch list.
 - Dispatch list not submitted to the RMS.
 - Declaration that the relevant national fees have been paid at the time of submission is missing in the RMS submission.
 - Misinterpretation of what changes can be grouped applied in one application for as consequential changes and what should be applied for as parallel variations.³
 - ~~Several not consequential changes are applied for in one application (eg. Update of several CEP's, deletion of several manufacturers⁴).~~
 - ~~Type IA/IB variations: The relevant conditions are not fulfilled (eg. condition: "The change relates only to standard immediate release oral pharmaceutical forms and to non-sterile liquid forms" is ticked for a semi-solid preparation for cutaneous application).~~
 - Type IA notifications: The relevant conditions are not fulfilled (eg. condition: "The change relates to standard immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms" is ticked for a semi-solid preparation for cutaneous application).
 - Variation C.I.1.b, C.I.2.a, C.I.3.a as type IB variation: Confirmation is missing that SmPC, PIL, labelling have been adapted identically to the reference text without any other changes (cf. CMDh Q&A 3.5 for variations).
 - A "z) Other" variation is submitted as a Type IA variation without an Article 5 recommendation.
 - The documentation package is incomplete with necessary information missing:
For example:

³ Guidance on groupings are given in the CMDh paper: Examples for acceptable and not acceptable groupings for MRP/DCP products:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_173_2010_Examples_groupings.pdf

⁴ Cf. CMD(h) Questions and Answers for the submission of Variations according to commission regulation (EC) 1084/2003:

- National translations are missing (for type IA and IB notifications) both annotated and clean versions.
 - References missing, expert statement missing (for type II variations).
 - Environmental risk assessment or justification for absence missing (for type II variations with extension of indication).
 - Uppdated product information is missing (when applicable) both annotated and clean versions.
 - Letter of authorisation/Power of attorney not attached if the name and address of MAH contact is different from the one approved.
 - The legibility of the documents, particularly PIL and labelling mock-ups, is poor.
- Product information in electronic format not submitted (when applicable).
 - Insufficient number of copies submitted (cf. Notice to Applicants, Chapter 7).