EXAMPLES FOR ACCEPTABLE AND NOT ACCEPTABLE GROUPINGS FOR MRP/DCP PRODUCTS

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For future variation applications comparable to those listed below as acceptable groupings applicants do not have to contact the RMS for acceptance as these grouped applications are already accepted by all EU member states.

As a general rule, type IA or IA\textsubscript{IN} variations for the implementation of safety-relevant changes may not be grouped together with type IB or type II variations as this would delay the implementation of this safety-relevant information.

1. ACCEPTABLE GROUPINGS

- All minor notifications of type IA and type IA\textsubscript{IN} may be grouped in one application without any relation to each other, if the group includes only type IA and type IA\textsubscript{IN}.
- Only notifications of type IA or IA\textsubscript{IN} may be grouped for more than one MA.
- After a transfer of the MA in one or more member states to a new MAH – which itself is an independent purely national application – all other changes related to that transfer, e.g. change in product name in that member state, new DDPS (see also Q/A 2.8 on Variations) or summary of pharmacovigilance system for the new MAH etc. may be grouped in one application according to the highest variation type for the single changes.
- In connection with the introduction of a new manufacturing site for the finished product other changes, e.g. changes in batch size, manufacturing process, including in-process controls etc., changes in site responsible for packaging (primary and secondary), batch release and quality control may be submitted in one application as a grouped variation according to the highest variation type for the single changes. For addition of a new finished product (FP) bulk manufacturing site also see 3 Acceptable as Single Change Instead of Grouping.

All these changes are regarded as belonging to the same project as described in Annex III of the Regulation “All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substance”.

- Addition of more than one pack size, where at least one of the proposed pack sizes is outside the range of currently approved pack sizes.
  - The update of an Active Substance Master File and any consequential changes to the active substance and if relevant finished product specifications (see also Q/A 3.4). For the update of an ASMF or Module 3.2.S (human)/respective sections in Part II (veterinary) also see 3 Acceptable as Single Change Instead of Grouping.
  - The update of the finished product specification (limits and analytical procedures)
• The update of the method of manufacture of the active substance (supported by ASMF or as part full dossier) and any consequential changes to the active substance and if relevant finished product specifications.
• Changes in the manufacturing process of the finished product including batch size, in-process controls etc. may be submitted in one application as a grouped variation.
• Changes to the composition of the finished product and if relevant any related changes to the method of manufacture, finished product specification (limits and analytical procedures), shelf life and storage conditions and product information (SmPC, label and PL).
• Changes to the primary packaging of the finished product in relation to qualitative/quantitative composition, dimensions, if relevant supplier and pack sizes, if related.
• Changes to the shelf life and storage conditions of the finished product.
• Changes to the re-test period and storage conditions of the active substance.
• Changes in primary packaging or to include a new primary packaging of the finished product is proposed (under category B.II.e.1 (a.1/2/3/4 or b.1/2) and related changes, etc to set different shelf-life and/or storage conditions for the new presentation of the medicinal product with respect to the currently authorized one (under category B.II.f.1)
• Changes in primary packaging or to include a new primary packaging of the finished product (under category B.II.e.1 (a.1/2/3/4 or b.1/2) and related changes, e.g. different specification parameters and/or limits and/or test procedures for the immediate packaging of the finished product are applied, and/or a new supplier of packaging components B.II.e.2/3 and/or B.II.e.7.
• Several changes of in-process controls may be submitted in a grouped application, each change according to the suitable classification in the classification guideline.
• Any updates to the pharmacovigilance system.
• Updates in line with the conclusions of a PSUR work sharing or PSUSA procedure (e.g. as an agreed Core Safety Profile) (human: C.I.3.b or z, veterinary: C.I.4 or C.I.4.z) and brand leader/innovator product (C.I.2.a or b).
• Changes following assessment of a given PSUR worksharing or PSUSA procedure (human: C.I.3b or z, veterinary: C.I.4 or C.I.4.z) (Regulation Annex III – example 11).
• Updates in line with PRAC/CMDh agreed wordings relating to a class (Regulation Annex III – case 10)/specific active substance (C.I.3.b or z)
• Updates in line with the Company Core Safety Information, provided the changes are related. If the CCSI has been updated in accordance with other recommendations or assessments, e.g. PSUR-WS, PSUSA, Paed WS etc., each of these recommendations triggers one single variation which may then be submitted as a grouped application to adapt to the CCSI. Every single change has to be classified according to the classification guideline.
• Updates in line with the brand leader/innovator (C.I.2.a or b) and NCA recommendations following the review of a PSUR worksharing or PSUSA procedure (human: C.I.3.b or z, veterinary: C.I.4 or C.I.4.z)
• Updates in line with Paediatric Worksharing (C.I.3.z) and PRAC recommendations / wording for the SmPC and PL (C.I.3.z), provided there is no delay to the implementation of the outcome of the PRAC recommendations and no additional data are submitted. (Q&A 4.13).
• Updates in line with the Company Core Safety Information and related changes, which are independent of the CCSI, following a further review of current literature e.g. National Formulary in relation to safety information. If the CCSI has been updated in accordance with other recommendations or assessments, e.g. PSUR-WS, PSUSA, Paed WS etc., each of these triggers one single variation which may then be submitted as a grouped application to adapt to the CCSI. Every single change has to be classified according to the classification guideline.
• Updates in line with the minimum clinical particulars for a product/class, recommendations made during assessment of a renewal (as type IB under C.I.z).

• Updates in line with the brand leader/innovator/reference product and the excipients guideline (which impact the content of the dossier) (grouped application C.I.2 (a or b) and C.I.z (Type IB/II)), see also Q/A 3.11).

• Update in line with agreed Core Safety Profile (or product information updates from PSUR work sharing or PSUSA), excipients guideline and QRD template (which impact the content of the dossier) (grouped application according to (human: C.I.3.z, veterinary C.I.4.z) and other categories in the classification guideline for every single change. If the CCSI has been updated in accordance with other recommendations or assessments, e.g. PSUR-WS, PSUSA, Paed WS etc., each of these triggers one single variation which may then be submitted as a grouped application to adapt to the CCSI.

• Updates in line with different guidelines affecting a product and impacting the content of the dossier e.g. SmPC, excipient and QRD template guidelines and any published agreed core SmPCs (C.I.z and human: C.I.3, veterinary: C.I.4 as type IB or type II).

• Class labellings agreed by the CMDh should be submitted under (C.I.3.z).

In case that more than one class labelling text agreed by CMDh relate to the same marketing authorization, these can be submitted as a grouped application consisting of several (C.I.3.z) variations. It is also possible to submit the other categories listed under (C.I.3.z) as a grouped application, provided that they apply to the same marketing authorisation. The implementation of safety information that needs to be implemented urgently should not be delayed due to grouping with other variations.

• All single changes concerning classification category (human: C.I.3.z, veterinary: C.I.4.z) can be submitted within one grouped application, provided that the implementation of safety information that needs to be implemented urgently is not delayed due to grouping with other variations. These changes of (human: C.I.3.z, veterinary: C.I.4.z) may also be combined with other changes of category C.I.2 within the same grouped application under the condition that the changes applied for are already harmonised and approved for the originator in the EU.

• After a member state has triggered an Art. 50 procedure of the Treaty on European Union several changes to the finished product might be necessary, e.g. changes to MAHs, manufacturers for batch release, new summary of pharmacovigilance system (human)/pharmacovigilance system (veterinary) in case of MAH transfers or changes in the product names etc. While the transfer of the MA to a new MAH is an independent purely national application all other changes related to the consequences of this Art. 50 procedure, may be grouped in one application according to the highest variation type for the single changes.

2. **NOT ACCEPTABLE GROUPINGS**

• Introduction of a new API manufacturer with a new ASMF may not be grouped with other unrelated quality changes concerning the active substance or the finished product but have to be submitted as separate applications.

• Variations for several minor changes of type IA and type IB though related to each other may not be grouped for more than one MA. In these cases a worksharing procedure should be followed.

• Changes to module 3 may not be grouped with a change in the product name if there is no relation between these changes and a common assessment is not justified. In exceptional cases where the

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1 Purely editorial changes can automatically be included as part of another variation to the same part of the dossier, provided that they do not change the actual content of the dossier and therefore the meaning of any text. This also includes editorial changes to the SmPC (see also Q/A 3.16).
changes to module 3 and the change in the product name are related with each other, e.g. changes in flavour, a grouping would be acceptable. However, the applicant should liaise with the RMS before submission.

- The combination of more than one acceptable grouping if the groups are not directly related with each other.
- The inclusion of unrelated Quality, Non-Clinical and Clinical changes.
- The inclusion of additional non-related changes to an already agreed grouping.
- The inclusion of a new active substance manufacturer as part of a variation to introduce a new finished product manufacturer.
- The inclusion of changes to the active substance and finished product, unless they are totally related.
- The inclusion of a safety related change that would delay its implementation.
- Addition or change of several active substance manufacturers that do not fully meet the Type IA conditions and documentation requirements.

3. ACCEPTABLE AS SINGLE CHANGE INSTEAD OF GROUPING

- The update of the dossier in preparation of a Repeat Use Procedure or MRP or before submission of a duplicate application may be submitted as one single application according to type II rather than a grouped application. The change may be introduced under classification category C.I.z – Update of the dossier in preparation of a RUP/MRP/duplicate application. This type II variation may include User Test, Braille, Environmental Risk Assessment, summary of pharmacovigilance system (human)/pharmacovigilance system (veterinary), RMP, QPs declaration, updated confirmatory stability data, updated Clinical and Non-clinical overviews and summaries (human)/expert reports (veterinary) based on already submitted and approved clinical and preclinical data. In case new data are submitted, for example the addition of literature references, separate variations for Modules 4 and 5/Part III and IV should be submitted. A grouped variation might be feasible if justifiable and agreed by the competent authority.

- The update of an ASMF – including changes of the open as well as the restricted part – or Module 3.2.S (human)/respective sections in Part II (veterinary) can be submitted as a grouped application according to the highest type of the single changes, if condition 5 or 6, respectively, of Annex III of the Variation Regulation applies. However, in case of substantial changes in the updated version of the ASMF or Module 3.2.S (human)/respective sections in Part II (veterinary) it is recommended to submit a single variation of type II under category B.I.z. However, it is a prerequisite for the validation of these single variations that the section “present/proposed” is filled out completely and correctly.

- For a change in the shape/dimensions of a tablet/capsule (B.II.a.2 – a or b) or a change/addition of imprints/markings (B.II.a.1 – a or b) a consequential change is e.g. in the finished product specification “appearance” and the corresponding IPC are modified. The submission of these changes in total are acceptable as a single variation under the a.m. category.

- When adding/changing a colouring agent (B.II.a.3.a) consequential changes as e.g. the finished product specification in respect of appearance/odour/taste and if relevant, deletion of an identification test are regarded as part of this variation and may be submitted as a single variation procedure.

- Addition of a new finished product (FP) bulk manufacturing site: changes to the manufacturing process, batch size and in-process controls to adapt to the new manufacturing site settings may be submitted as single type II variation under B.II.b.1 according to the indent of the main change but updated to type II. Complex related changes submitted under a single type II should always be clearly identified in the application form as following: a clear description of all the consequential changes should be provided in the precise scope. All the related changes should be listed in the present/proposed table. Changes affecting the FP and not only related to the introduction of the new
Examples for acceptable and not acceptable groupings for MRP/DCP products

In case more than one manufacturer in one MA has to be deleted a single variation of type IA under classification category A.7 to delete all manufacturing sites may be submitted. However, it has to be assured that there is still one approved manufacturing site left in the documentation performing the same function as the one(s) concerned by the deletion.

A change in the name of a manufacturing site responsible for batch release AND other activities may be submitted as a single application as per scope A.5.a), type IA-IN.

Changes to the product information resulting from comments of the new CMS during a repeat use procedure should be applied for in one single type II variation under category C.I.z and submitted to the RMS and all CMS. Editorial changes can be made according to Q/A 3.16.

Veterinary: Changes to the product name in several MS: See CMDv RfR 3-4/2016

A change in MAH’s active substance specification which follows a change in CEP, ASMF or API details is accepted as a single variation provided that the conditions in the guideline are considered (i.e. upgrade to type IB when condition on same specification is not met) (cf. CMDh minutes September 2016 and CMDv RfR Oct-Nov 2016).