EUROPEAN GENERIC MEDICINES ASSOCIATION

POSITION PAPER

SUBMISSION OF COMMENTS ON 'GUIDELINE ON THE DETAILS OF THE VARIOUS CATEGORIES OF VARIATIONS'

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The EGA is the official representative body of the European generic and biosimilar pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

Introduction:

The European Generic medicines Association (EGA) appreciates the opportunity to comment on the revised Variations Classification guideline. For EGA members, usually having very large portfolios, a rational and cost-efficient variations system is crucial. A number of the proposed changes are positive and bring good solutions to reporting variations. However, we believe that there is still room for further improvement.

Cost/ **effectiveness of the system:**

- The current revision of the guideline coincides with the implementation of the new Pharmacovigilance legislation. The introduction of new elements (like the Pharmacovigilance Master File, Summary of the PhV system, changes in the PSURs cycle etc) should be implemented in a very rational and pragmatic way to assure not only better protection of the public health but also to follow the principle of better regulation initiative, launched by the EC in 2005 which is supposed to deliver concrete benefits for businesses and competitiveness by reducing costs and the administrative burden for the industry. In the EC impact assessment in 2008, the implementation of the new PharmacoVigilance legislation was supposed to bring overall cost savings of € 145 Million per year to the EU industry sector. This must be kept in mind in view of the practical implementation, including the changes suggested to be reported via the official variation process. All transitional arrangements related to moving into new Pharmacovigilance rules must be very pragmatic and the formal variations must be avoided as much as possible. Otherwise the costs and workload associated with these processes are unsustainable for the industry. As an example, for the introduction of a summary of the Pharmacovigilance system as it is in the guideline now, the estimated costs for a bulk variation can be up to €7 mio for large companies, although the assessment will be the same for one product as for 20 000 products.
- Although fees remain a purely national issue and are out of the scope of this consultation, the EGA members urgently call on the Member States to apply a fees policy which reflects whether real **assessment is needed** or not (e.g. particularly for administrative changes, or the same information already being in the possession of authorities but called differently), whether **the same change applies to several products** etc. The fees system **should better distinguish between individual product related changes and the company's related changes** which apply to several or even all products of the MAH. Further reflection is also needed on **counting the grouped variations' fees in view of the next revision of fees** by the EC as well as the next revision of fee regulations at the level of the MS.
- The high fees for the submission of variations to the MAs **should not become a barrier to improving various aspects of medicinal products** (e.g.

improvement of quality, more harmonised information to patients, implementation of the latest knowledge on safety profile etc.). Otherwise the objective of the last revision of the Variations Regulation is not met.

Terminology:
Harmonisation of language appears necessary to minimise risk of diverging interpretation: Minor, Major , Substantial, conventional, non conventional complex manufacturing process, enhanced development approach, critical parameters, in-process tests, in process limits etc.

Procedural aspects:
In the current regulation IA and IAIN cannot be submitted during running renewal procedures. In practice renewal procedures may take from several months up to more than 1 year. Considering IA variations are to be submitted within one year after implementation this practice poses an inherent risk of incompliance. Considering additionally that IA and IAIN variations reflect minor changes with low impact on safety, efficacy and quality, this practice requires to be changed. Submission of IA and IAIN should also be possible during pending renewal procedures.

Discussion with the industry prior the final adoption of the guideline:
In view of the significant number of comments and importance of this guideline for the industry's daily work, it would also be recommended that there is an open dialogue with the Commission and other stakeholders on the revision to this guideline in advance of the final adoption. This would be greatly facilitated by a workshop led by the Commission to discuss major comments in further detail.

The EGA internal consultation led to a large number of comments. In order to prioritise comments, those of **higher importance have been highlighted in light blue.**

Variation number	Currently proposed or revised change	Comment	EGA proposal
A. Administrative changes			
A.1	Change in the name and/or address of the marketing authorisation holder (Type IA_{IN})	The change in the name and/or address of the MAH should only be processed in the relevant MS(s), at national level. ***Justification*** In MRP/DCP, the transfer of the MA to a new MAH is handled at the national level, only in the relevant MS(s). To inform all countries about the change irrelevant to them appears unnecessary administrative burden.	Add the following note: **'Note: For products registered via MRP/DCP, the MAH can notify only the Member State(s) concerned by the change of address.'**
A.3	Change in the name of the active substance ***or of an excipient.***	Further clarity should be provided on the change in the name of excipients. ***Justification*** The change could cover the monograph name, chemical name, INN or all such instances	Add a note which clarifies the changes covered in the case of excipients.

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A.4	Change in the name and/or address of a manufacturer (including where relevant quality control ***testing*** sites***),*** ***ASMF holder,*** or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier ***or a manufacturer of a novel excipient***.	Even though the name/address of the ASMF holder is routinely included in 3.2.S.2.1 and 1.2, update of this should not be considered a variation. ***Justification*** It is not clear why a change in the ASMF holder name/address would constitute a variation as long as the manufacturing site name/address remains the same.	Delete ASMF holder from the proposed revision: Change in the name and/or address of a manufacturer (including where relevant quality control ***testing*** sites***),*** ~~***ASMF holder,***~~ or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier ***or a manufacturer of a novel excipient***.

Variation number	Currently proposed or revised change	Comment	EGA proposal
A.4	Change in the name and/or address of a manufacturer (including where relevant quality control ***testing*** sites***),*** ***ASMF holder,*** or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier ***or a manufacturer of a novel excipient.***	Based on current experience, the change in the name of an active substance manufacturer can be done at the same time as the addition of a new CEP from an already approved manufacturer. ***Justification*** As the change in name is permitted as part of the CEP variation a separate variation to change the name is not applicable in these cases.	Change in the name and/or address of a manufacturer (including where relevant quality control ***testing*** sites***),*** ***ASMF holder,*** or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is ~~part of the approved dossier~~ **available** ***or a manufacturer of a novel excipient.***
A.5.b	Change in the name and/or address of a manufacturer of the finished product including ***importer, batch release or*** quality control ***testing*** sites b) All other ***(including supplier of packaging components or devices (where specified in the product dossier))***	This variation does not read simply. Primary and secondary packaging sites should be included in the title so that it is clearer. Documentation requirement 1 should be reinstated for (b). It is not clear why documentation number 1 has been deleted from A.5.b.	Please reword and clarify which category (A.5.a or A.5.b) would be suitable for changes relating to packaging site.

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A.7	Deletion of manufacturing sites Condition *3. At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able carry out product testing for the purpose of batch release within the EU/EEA.*	Condition 3 appears self-evident to fulfil the requirements allowing EU batch certification and/or release.	

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.I Quality changes to the active substance			
B.I.a) Manufacture			
B.I.a.1	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control ***testing*** sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	In case of structurally well-defined APIs no manufacturers of reagents (e.g. NaOH, HCl,….) are usually part of the registration documentation, therefore it is recommended to include the following sentence for clarification "(when mentioned in the dossier)" in analogy to item A.7.a)	Amend to: Change in the manufacturer of a starting material/ reagent/ intermediate **(when specified in the dossier)** used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control ***testing*** sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.I.a.1	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control ***testing*** sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	This variation should be broadened so that other situations where the exact same route of synthesis is used are covered. ***Justification*** The current proposed wording does not cover the common situation whereby an API is produced through a contract manufacturing organisation (i.e. outside the same pharmaceutical group) according in accordance with the detailed route of synthesis as already approved.	Amend a) as follows: a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer **or is a contract manufacturing organization using the same route of synthesis as the pharmaceutical group**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.I.a.1	Change in the manufacturer of a starting material/ reagent/ intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control ***testing*** sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer Condition 1. For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.	Condition 1 (Type IA_{IN}) for a change in supplier for starting materials and reagents being part of the same pharmaceutical group requires identical specification (including in process controls, methods of analysis of all materials). For structurally well-defined APIs, in-process controls and acceptance criteria, methods of analysis of all materials used in the manufacture of starting materials and reagents are usually not part of the registration dossier. For reagents refer to the comment above for B.I.a.1 Change in the manufacturer of a …./reagent/…	Change Condition 1 to Condition 1. For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved. **For starting materials used in the manufacture of structurally well-defined APIs the route of synthesis is identical to that already approved (no new raw materials, reagents, and solvents).**

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B.I.a.1	Change in the manufacturer of a starting material/ reagent/ intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control *testing* sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier ***g) Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier (new Type II)***	The term "significant update" is not very specific and should be better defined.	Please clarify.
B.I.a.1	Change in the manufacturer of a starting material/ reagent/ intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control *testing* sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier ***h) Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method*** Documentation *8. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.:* *For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A*	We would recommend the following wording to allow covering a broader range of changes and give a clearer understanding. The variation concerns a change in sterilization site for the active substance and therefore, a declaration by the Qualified Person that the site is appropriately authorized seems the right level of documentation.	***h) Replacement or Addition of an alternative sterilisation site for the active substance using a sterilisation method described in the Ph.Eur. ~~method~~*** ***8. Declaration by the Qualified Person (QP) that the proposed site is appropriately authorised fro the pharmaceutical form or ^product or manufacturing operation concerned. ~~Proof that the proposed site is appropriately authorised for the pharmaceutical form or~~***

Variation number	Currently proposed or revised change	Comment	EGA proposal
	reference to the EudraGMP database will suffice. *For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority.* *For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.*		~~*product or manufacturing operation concerned, i.e.:*~~ ~~*For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice.*~~ ~~*For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority.*~~ ~~*For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.*~~

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.I.a.1	Change in the manufacturer of a starting material/ reagent/ intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control ***testing*** sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier ***j) Changes to quality control testing arrangements for a biological active substance-replacement or addition of a site where batch control/testing including a biological / immunological / immunochemical methods takes place***	In our opinion this variation could also be rated as an IB item. Possible concern should be mentioned as conditions.	Please modify the classification to IB.

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B.I.a.1	Change in the manufacturer of a starting material/ reagent/ intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control *testing* sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier ***k) New storage site of Master Cell Bank and/or Working Cell Banks***	In case of classical fermentation products the information related to the storage site for Master Cell Bank and / or Working Cell Banks is in our experience not part of the registration documentation. Please note that it is moreover current industry practice to split cell banks onto two sites as a preventing measure in case of emergencies (e.g. natural disaster). ***Justification*** The relevant information included in the registration file relates to the storage conditions rather than the actual storage site. The information relating to the storage site is of no relevance so long as the same storage conditions as currently already registered and proven as safe are applied.	Downgrade to IA. Amend as follows: Change in the manufacturer of a starting material/ reagent/ intermediate **(when mentioned in the dossier)** used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control *testing* sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier ***k) New storage site of Master Cell Bank and/or Working Cell Banks***

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B.I.a.2	Changes in the manufacturing process of the active substance *f) Change to non-critical processes parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing step(s)* Conditions *8. The manufacturing process has been developed using an acknowledged enhanced development approach and the changes only concern non critical process parameters.* *9. The effect of the proposed change has been evaluated using an already approved monitoring scheme and the process parameter in question remains non critical*	The term "(acknowledged) enhanced development approach" should be clarified. The term "process parameters" should be changed to "in-process test".	Add a Note referring to ICH Q8 Pharmaceutical Development and/or Q11 Development and manufacture of drug substances (chemical entities and biotechnological / biological entities) and their respective glossary to ease understanding. Please harmonise the terminology accordingly.
B.I.a.2	Changes in the manufacturing process of the active substance Documentation ***5. Documentary evidence that, that the non-criticality of the parameter has been accepted as part of a previous assessment where the enhanced development approach in the development and optimisation of the manufacturing process concerned is formally acknowledged.***	'Documentary evidence' is not a common regulatory term and should be further clarified.	Please explicit this term or replace by well-known regulatory terminology.

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B.I.a.2	Changes in the manufacturing process of the active substance b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product	This variation should explicitly refer to substantial changes to the manufacturing process of the active substance which do not have a significant impact on the quality, safety or efficacy of the medicinal product.	Add: **g) Major change to the manufacturing process of the active substance which do not have a significant impact on the quality, safety or efficacy of the medicinal product.** **Type IB** **Documentation 10** **Documentation** **10. Justification that the change does not affect the quality, safety or efficacy of the medicinal product**
B.I.a.2	Changes in the manufacturing process of the active substance e) Minor change to the restricted part of an Active Substance Master File	This variation should explicitly refer to major changes to the restricted part of an Active Substance Master File	Add: **h) Major change to the restricted part of an Active Substance Master File** **Type II**

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B.I.a.2	Changes in the manufacturing process of the active substance Documentation 3. Copy of the approved specifications of the active susbtance	Documentation 3 maybe deleted from B.I.a.2.a and B.I.a.2.f ***Justification*** Documentation 3 appears unnecessary when condition 3 is fulfilled as the unchanged approved specifications are already available in the dossier.	Delete documentation 3 from B.I.a.2.a and B.I.a.2.f
B.I.a.3	Change in batch size (including batch size ranges) of active substance or intermediate ***used in the manufacturing process of the active substance*** a) Up to 10-fold increase compared to the currently approved batch size Condition 8. The currently approved batch size was not approved via a Type IA variation	Condition 8 is restrictive and requires further clarification. ***Justification*** It should not be possible to scale up from 1kg to 9kg (x9) by Type IA and then again to 15kg by Type IA and so in effect increase the batch size by x15 from what was originally approved by the submission of two Type IA variations (without regulatory assessment). However it should be acceptable to submit two Type IA variations to increase the original batch size first to 5kg and then to 9kg as the final batch size remains within the requirement of 'up to 10-fold of the original batch size.	Amend a) and Condition 8 as follows: a) Up to 10-fold increase compared to the **originally** ~~**currently**~~ approved batch size 'The currently approved batch size was not approved via a Type IA variation. ***Not applicable if the proposed batch size remains within 10-fold of the originally approved batch size'***
B.I.a.4	Change to in-process tests or limits applied during the manufacture of the active substance ***g) Change to the limits of non-critical processes parameters, where the process has been developed***	The term "(acknowledged) enhanced development approach" should be clarified.	Add a Note referring to ICH Q8 Pharmaceutical Development and Q11 Development and manufacture of drug substances (chemical entities and

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	and optimised using an enhanced development approach for the particular manufacturing step(s). Conditions *7. The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.* *8. The manufacturing process has been developed using an acknowledged enhanced development approach and the changes only concern non critical process parameters.* *9. The effect of the proposed change has been evaluated using an already approved monitoring scheme and the process parameter in question remains non critical.*	The term "process parameters" should be changed to "in-process test".	biotechnological / biological entities) and their respective glossary to ease understanding. Please harmonise the terminology accordingly.

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B.I.a.4	Change to in-process tests or limits applied during the manufacture of the active substance Documentation ***7. Documentary evidence that, that the non-criticality of the parameter has been accepted as part of a previous assessment where the enhanced development approach in the development and optimisation of the manufacturing process concerned is formally acknowledged.***	'Documentary evidence' is not a common regulatory term and should be further clarified.	Please explicit this term or replace by well-known regulatory terminology.
B.I.a.4	Change to in-process tests or limits applied during the manufacture of the active substance a) Tightening of in-process limits b) Addition of a new in-process test and limits c) Deletion of a non-significant in-process test	The variation should cover all types of minor changes to an in-process test or limit equally. ***Justification*** The description of the variation and the fulfilment of condition 4 seem to allow minor changes however other minor changes than those captured here could be eligible for type IA classification (rather than IB by default).	Add the following: ***h) Other minor change in an in-process test procedure.*** ***Type IA provided Conditions 1, 2, 3 and 4 are fulfilled.***

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B.I.a.4	Change to in-process tests or limits applied during the manufacture of the active substance d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance	The current classification should cover situations in which widening the approved in process test limits does not have a significant effect on the overall quality of the active substance.	Add the following: **h) Widening the approved in process test limits which do not have a significant effect on the overall quality of the active substance.** **Type IB** **Provided Documentation 10 is available** **Documentation 10** **Justification for not having a significant effect on the overall quality of the active substance**
B.I.b) Control of Active Substance			
B.I.b.1	Change in the specification parameters and/or limits of an active substance / starting material /intermediate /reagent used in the manufacturing process of the active substance a) Tightening of specification limits for medicinal products subject to Official Batch Release	The terminology 'Official Batch Release' needs to be changed to 'Official Control Authority Batch Release'. ***Justification*** This is applicable to biological products only and is the current wording.	Please change accordingly

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B.I.b.1	Change in the specification parameters and/or limits of an active substance / starting material /intermediate /reagent used in the manufacturing process of the active substance ***i) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country***	This variation should cover changes (e.g. updates) of non-official/third country pharmacopoeia (e.g. USP)	Amend as follows: ***i) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country (e.g. updated monograph)***
B.I.b.2	Change in test procedure for active substance or starting material/ reagent/ intermediate used in the manufacturing process of the active substance	This variation pertains to change in test procedure for……reagents ……..used in the manufacturing process of the active substance. In case of structurally well-defined APIs no test methods for reagents (e.g. NaOH, HCl,….) are usually part of the registration documentation (only acceptance criteria), therefore it is recommended to include the following sentence for clarification '(when mentioned in the dossier)' in analogy to item A.7.a).	Change to: Change in test procedure for active substance or starting material/ reagent/ intermediate **(when mentioned in the dossier)** used in the manufacturing process of the active substance

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B.I.b.2	Change in test procedure for active substance or starting material/ reagent/ intermediate used in the manufacturing process of the active substance	See general comment on changes to the restricted part of the ASMF after introduction of an EU numbering system.	Add: **Note: After implementation of the revised approach to ASMF assessment (EMA guideline).** **Submission of changes to the restricted part of the dossier will be classified as IA (not requiring assessment).**
B.I.b.2	Change in test procedure for active substance or starting material/ reagent/ intermediate used in the manufacturing process of the active substance ***d) Substantial change to or*** replacement ***of*** a biological/ immunological/ immunochemical test method or a method using a biological reagent for a biological active substance	Please use the standard terminology applicable to variations i.e. Major, minor	Amend accordingly
B.I.b.2	Change in test procedure for active substance or starting material/ reagent/ intermediate used in the manufacturing process of the active substance	Add a sub-category reflecting possible changes to test procedures according to other Pharmacopoeias as applies for B.I.b.1).i)	Add: **f) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in testing method from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country."** **Type IB**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.I.d) Stability of Active Substance			
B.I.d.1	Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	There is no listed variation covering the possibility to extrapolate data in accordance with ICH/VICH guidelines.	Add **a) 5. Extension of the re-test period based on extrapolation of stability data in line with ICH/VICH guidelines** **Type IB.**
B.I.d.1	Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	There is no listed variation covering the possibility to reduce testing frequency in an approved stability protocol.	Add **d) Reduction of testing frequency in an approved stability protocol** **Condition 2** **The reduced frequency does not have any influence on the re-test period.** **Documentation 5** **Justification of the frequency reduction**

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B.I.f) Post-Approval change Management Protocols			
B.I.f.3	***Changes to an approved post approval change management protocol related to the active substance*** ***b) Minor changes to an approved post approval change management protocol that do not change the strategy defined in the protocol*** Condition ***1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/ immunological medicinal products.***	This category refers to minor changes in the protocol and requires the submission of a declaration that any change should be "within the range of currently approved limits". We do not believe that such a declaration will be appropriate for all minor changes hence a revised documentation wording needs to be sought.	

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B.I.g) Multiple changes to an ASMF			
The introduction of a new variation category to cover multiple changes to an ASMF should be considered to ensure an appropriate assessment of the proposed changes, while removing the complexity for both authorities and industry to try and list each single change. A possibility for Type IB variation to make administrative updates to the ASMF to make it current including adding 'non-registered' details such as updated batch data, updated stability data (without request to extend the retest period), data already assessed and agreed during RTQ, etc. In a case of multiple minor variations to the ASMF which are described in detail in part **B.I ACTIVE SUBSTANCE** (for example manufacture, raw materials, stability etc..) we suggest to **add** the possibility for applicants to submit an updated ASMF including the list of changes, as a single Type II variation. For clarity we would propose that this should be a separate category under B.I. This approach has been proposed as an option by the DKMA on their website. **Assessment of the ASMF:** Under the new ASMF assessment procedure guidance (and complementing guidance documents), it will soon be possible to cross-refer to already approved ASMFs, which will have a unique mandatory EU numbering system. Therefore, submission of a IB variation (requiring assessment) of changes to the restricted part of the ASMF may no longer be relevant, as the changes may have already been assessed. There should be a IA variation category foreseen so that the applicant can notify the competent authorities that the restricted part has been updated and already assessed. It should preferably be prospectively introduced (as for the data under art 57- once the numbering and the worksharing systems are in place).		

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B.II Quality changes to the finished product			
B.II.b Manufacture			
B.II.b.1	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product Documentation 4 Copy of the approved release and end-of-shelf life specifications if relevant.	Documentation 4 would be more specific if reference was made to the specifications of the "new site"	Amend Documentation 4 Copy of approved release and end-of-shelf life specifications **from the new site**, if relevant
B.II.b.2	Change to ***importer,*** batch release arrangements and quality control testing of the finished product	There does not seem to be an EU definition for importer. It is also unclear whether the introduction of an 'importer' in the dossier is relevant or necessary. EGA members report having encountered different opinions across EU member states. In the absence of clarity, considering the need for variations related to importers could potentially cause administrative burden.	We recommend deleting the term importer until the CMD(h) or EC have clarified the applicable definition and requirements (i.e. in the dossier or not) for importers.

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B.II.b.2	Change to *importer*, batch release arrangements and quality control testing of the finished product Condition *5. At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able carry out product testing for the purpose of batch release within the EU/EEA.*	Condition 5 appears self-evident to fulfil the requirements allowing EU batch certification and/or release.	
B.II.b.2	Change to *importer*, batch release arrangements and quality control testing of the finished product b) Replacement or addition of a *site where* batch *control/testing takes place for a biological/ immunological product and one of the test methods performed at that site is a biological / immunological / immunochemical method*	Could you please clarify if this category means biological product and/or a least one biological method?	
B.II.b.2	Change to *importer*, batch release arrangements and quality control testing of the finished product *c) Replacement or addition of a manufacturer responsible for importation and/or batch release* 2. Including batch control/testing	This variation is a Type IA_{IN} in the current classification guideline; the change to a Type II is quite surprising and does not appear justified. We believe that is a just a typing error.	Amend the classification back to a Type IA_{IN}.

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.b.3	Change in the manufacturing process of the finished product, ***including an intermediate used in the manufacture of the finished product***	Changes relating to the holding time of bulk tablets need to be covered specifically in the variation classification. We recommend that these be classified as Type IB changes under the section B.II.f Stability as they relate more to stability changes than typical manufacturing changes.	Amend B.II.f accordingly
B.II.b.3	Change in the manufacturing process of the finished product, ***including an intermediate used in the manufacture of the finished product***	This variation category fails to specifically cover changes in the manufacturing process of non-immediate release oral products	Add a category for non-immediate release oral products
B.II.b.3	Change in the manufacturing process of the finished product, ***including an intermediate used in the manufacture of the finished product***	This variation category should cover substantial changes having no effect on Quality, safety and efficacy.	Add: **h) Major changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product** **Type IB** **Documentation 10** **10. Justification of the absence of a significant impact on the quality, safety and efficacy of the medicinal product**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.b.3	Change in the manufacturing process of the finished product, *including an intermediate used in the manufacture of the finished product* c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability	In line with the new active substance requirements (B.I.a.2. c) it should be possible to submit minor process changes (non-significant impact) for biological drug product as variation type IB.	Add: **h) Minor change to a biological/immunological medicinal product** **Type IB**
B.II.b.3	Change in the manufacturing process of the finished product, ***including an intermediate used in the manufacture of the finished product*** *g) Change to non critical processes parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing steps* Conditions *8. The manufacturing process has been developed using an acknowledged enhanced development approach and the changes only concern non critical process parameters.* *9. The effect of the proposed change has been evaluated using an already approved monitoring scheme and the process parameter in question remains non critical.*	The term "(acknowledged) enhanced development approach" should be clarified. The term "process parameters" should be changed to "in-process test".	Add a Note referring to ICH Q8 Pharmaceutical Development and Q11 Development and manufacture of drug substances (chemical entities and biotechnological / biological entities) and their respective glossary to ease understanding. Please harmonise the terminology accordingly.

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.b.4	Change in the batch size (including batch size ranges) of the finished product d) The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	Definition of 'complex manufacturing process' should be provided with reference to ICH (or other) guidelines if necessary. Definition of what is a complex process compared with non-standard process needs to be clear. Type IB are deemed sufficient under the condition that for pharmaceutical forms manufactured by complex manufacturing processes the results of process validation are required. The draft EMA guideline on Process Validation (EMA/CHMP/CVMP/QWP/ 70278/2012-Rev1) does not refer to the notion of 'complex manufacturing processes' and as such it is anticipated that unless 'complex' is defined there will be a lot of disharmony between and across applicants and competent authorities of what this term actually represents. For example a tablet could be considered 'non-standard' as the active content is low (<2%) but the manufacturing process 'standard / non-complex' as it is simple dry granulation.	Amend B.II.b.4.d) to a **Type IB** with reference to Condition 6

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.b.4	Change in the batch size (including batch size ranges) of the finished product a) Up to 10-fold compared to the currently approved batch size *Condition 2* 2. The change relates to conventional immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms. Condition 7 7. The currently approved batch size was not approved via a Type IA variation. ***For the first increase in batch size post initial authorisation for immediate release oral pharmaceutical forms for systemic action, the currently approved production batch size on which bioequivalence has been supported is at least 100,000 units or 10% of production scale batch size, whichever is greater, unless otherwise justified. For veterinary medicinal products the currently approved production batch size on which bioequivalence has been supported is at least 10% of production batch size, unless otherwise justified.***	'Conventional' should be defined (as for 'complex manufacturing process' above). What is the difference between 'conventional' and 'standard'? There should be a classification for up to 10-fold increase of non-conventional dosage forms as IB supported by the necessary documentation. Condition 7 requires further clarification. The rationale behind it is understood in that it should not be possible to scale up from 100,000 tablets to 1,000,000 (x10) by Type IA and then again to1,500,000 by Type IA and so in effect increase the batch size by x15 from what was originally approved by 2 x Type IA variations (no assessment). However it should be acceptable to submit 2 x Type IA variations to increase the batch size first to 500,000 and then to 900,000 as they both remain within x 10 of the original batch size.	Amend to: a) Up to 10-fold compared to the ~~currently~~ **originally** approved batch size 7. The currently approved batch size was not approved via a Type IA variation. ***Not applicable if proposed batch size remains within 10-fold of the originally approved batch size'*** For the first increase in batch size post initial authorisation for immediate release oral pharmaceutical forms for systemic action, the currently approved production batch size on which bioequivalence has been supported is at least 100,000 units or 10% of production scale batch size, whichever is greater, unless otherwise justified. For veterinary medicinal products the currently approved production batch size on which bioequivalence has been supported is at least 10% of production batch size, unless otherwise justified. ***g)* Up to 10-fold compared to the currently approved batch size for non-conventional dosage forms** **Type IB** **Documentation 1, 4, 5, 6**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.b.4	Change in the batch size (including batch size ranges) of the finished product	This variation needs to cover the cases where a new batch size is added (and not changed, i.e. replacing the current batch size)	Change in **or addition of a** batch size (including batch size ranges) of the finished product
B.II.b.5	Change to in-process tests or limits applied during the manufacture of the finished product b) Addition of a new tests and limits	Editorial change	We suggest to change the text as following: Addition of a new test~~s~~ and limit~~s~~

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.b.5	Change to in-process tests or limits applied during the manufacture of the finished product c) Deletion of a non-significant in-process test Condition *7. The in-process test does not concern the control of a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the excipient), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, unless there is a suitable alternative control already present, microbiological control, unless not required for the particular dosage form.*	Condition 7 - It should be considered acceptable to delete one of these IPCs (assay/related substance) as a Type IA variation if the process is validated and the test is still included in the release specification. Propose a category for widening of spec/IPC limits for non-critical parameters, not effecting quality/safety e.g. widening of tablet thickness. Type IB with addition of a justification document of why the change IPC is not critical to safety and efficacy. Nothwithstanding the above **condition 7** seems to have the **wrong text version** in brackets ("unless a particular solvent is no used in the manufacture of the excipient)" as this section is about in-process control and not excipients.	Amend to: 7. The in-process test does not concern the control of a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the excipient), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, unless there is a suitable alternative control already present, microbiological control, unless not required for the particular dosage form. **Alternatively the in-process test does concern the control of a critical parameter (as listed above) yet the process is validated and the test is used in the release specification.** Correct the text in bracket

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.b.5	Change to in-process tests or limits applied during the manufacture of the finished product *g) Change to the limits of non-critical process parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing step(s)*	Inconsistency of terminology	The term "process parameters" should be changed to **"in-process test".**
B.II.c Control of excipients			
B.II.c.1	Change in the specification parameters and/or limits of an excipient	As per previous comments propose to include a Type IB to delete a specification parameter / widen approved limits which is not 'non-significant' (category c) but will not have a significant effect (category e). Justification to be provided as supporting information.	Add: **h) Deletion or widening of a specific parameter not having a significant effect on the quality, safety or efficacy of the product.** **Type IB** **Documentation 9** **9. Justification that the change does not affect the quality, safety or efficacy of the product**
B.II.c.1	Change in the specification parameters and/or limits of an excipient c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	We propose to include "(e.g. odour)", in alignment with the statement for drug substance raw materials (B.I.b.1.d).	Amend to: c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter **(e.g. odour))**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.c.5	*Change in manufacturer of a novel excipient* *a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer* *b) Introduction of a new manufacturer of the novel excipient that requires significant update to the relevant novel excipient section(s) of the dossier* *c) Introduction of a new manufacturer of a biological novel excipient*	This change category should also cover changes in manufacturers of non-novel excipients (when mentioned in the dossier)	Amend to Change in manufacturer of a novel / **standard** excipient **(when mentioned in the dossier)** a)novel excipient 1. The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 2. Introduction of a new manufacturer of the novel excipient that requires significant update to the relevant novel excipient section(s) of the dossier 3. Introduction of a new manufacturer of a biological novel excipient **b) all changes for other excipients** **Type IA**
B.II.d Control of finished product			
B.II.d.1	Change in the specification parameters and/or limits of the finished product.	Since the introduction of skip testing is excluded from B.I.b.1 (condition 8.) it is assumed it will automatically be a Type IB variation but it would be useful to categorise it.	Add: **j) Introduction of skip testing into the product specification** **Type IB**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.d.1	Change in the specification parameters and/or limits of the finished product. g) Addition or replacement (excluding biological or immunological product) of a specification parameter, with its corresponding test method, as a result of a safety or quality issue (Type IB).	This category does not yet cover the possibility to replace a specification without it being a result of a quality / safety issue.	Amend: g) Addition ~~or replacement~~ (excluding biological or immunological product) of a specification parameter, with its corresponding test method, as a result of a safety or quality issue (Type IB). Add: **k) Replacement (excluding biological or immunological product) of a specification parameter, with its corresponding test method** **Type IB**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.d.1	Change in the specification parameters and/or limits of the finished product *h) Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product*	If reference to the current Ph.Eur, version is made in the dossier no variation is necessary to date if the changes are implemented within 6 months after publication of the update. This new change requires the submission of a variation for each monograph update and would increase the number of variations and does not add anything in respect to product quality/safety. It is also in contradiction to the note stated under B.III.2.	Add: h) Conditions1,2,3,4,7,8,**10,11** **Condition 10** **The change relates to a dossier were no reference to the current Ph.Eur., version is made.** **Condition 11** **The change is implemented more than 6 months after publication of the update.** Add: ***Note: There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product.***

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.d.1	Change in the specification parameters and/or limits of the finished product *i) Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass. or Ph. Eur. 2.9.6 (Uniformity of content)*	This is classified as a type IB variation. This change could be downgraded to a type IA change as this is a change from one Ph.Eur. method to another one with no significant impact on the product quality.	Change to: Type **IA**
B.II.d.1	Change in the specification parameters and/or limits of the finished product	This category of changes should cover the specific situation whereby the FP specifications are updated to comply with the Ph.Eur. as is the case for powders for injection where the FP is essentially the drug substance filled into vials.	Add: **j) Update to the specification to comply with Ph.Eur (e.g. for powders for injection where the FP is essentially the drug substance filled into vials)**
B.II.d.2	Change in test procedure for the finished product. *f) To reflect compliance with the Ph.Eur. and remove reference to the internal test method and test method number* Condition *5. The registered test procedure already refers to the general monograph of the Ph. Eur and any changes are minor in nature and require updating of the dossier information.*	This variation is not clear. Such variation would not be considered a variation if the dossier already mentions compliance to the Ph. Eur current version (as per comment above).	Remove B.II.d.2.f

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.e Container Closure System			
B.II.e.4	Change in shape or dimensions of the container or closure (immediate packaging)	This category should cover changes where the head space or surface / volume ratio remain unchanged.	Add **d) The change in shape or dimensions does not have a significant impact on the delivery, use, safety or stability of the finished product** **Type IA** **Conditions 1, 2, 3** **Documentation 1, 2, 5** **Documentation 5** **Justification that the head space or surface/volume ratio are unchanged.**
B.II.e.5.	Change in pack size of the finished product a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack 1. Change within the range of the currently approved pack sizes 2. Change outside the range of the currently approved pack sizes	Documentation requirement 4 has been added which actually describes more a **condition** than a documentation requirement. Besides the fact that this condition is self-evident since all packages have always to be of good quality (not really an RA issue but a quality one) what exactly would be expected to be added to the variation application here?	Amend Documentation 4 to: **Condition 4**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.II.e.6	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) a) Change that affects the product information		Amend Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) a) Change that affects the product information **(e.g. unit dose blisters, calendar packs, colour of flip-off caps)**
B.II.f Stability			
B.II.f.1	Change in the shelf-life or storage conditions of the finished product	There is no listed variation covering the possibility to extrapolate data in accordance with ICH/VICH guidelines.	Add **b) 6. Extension of the re-test period based on extrapolation of stability data in line with ICH/VICH guidelines** **Type IB.**
		Changes relating to the holding time of bulk tablets need to be covered specifically in the variation classification. We recommend that these be classified as Type IB changes under the section B.II.f Stability as they relate more to stability changes than typical manufacturing changes.	Add: **B.II.f.2 Change to the holding time of Bulk tablets and bulk solution (unfiltered and or filtered) of sterile injectables** **Type IB**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.III CEP/ TSE / monographs			
B.III		This section brings in a whole new load of new Type IA variations for the 'deletion of certificates'	
B.III.1	Submission of a new or updated Ph. Eur. Certificate of **suitability or deletion of Ph. Eur. certificate of suitability:** **For an active substance** **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient** a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. 5. Deletion of certificates (in case multiple certificates exist per material)	Such new change will significantly increase the administrative burden and create an unnecessary congestion of the regulatory system, and of its resources.	Delete this new variation

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.III.1	**Submission of a new or updated Ph. Eur. Certificate of suitability or deletion of Ph. Eur. certificate of suitability:** • **For an active substance** • **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** • **For an excipient** Condition 2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.	It is understood that impurities / solvent limits which are changed on an updated CEP (including addition / deletion of non-EP impurities or change in their limits) can be changed as part of the IA variation to update the CEP. As the impurity profile of the raw material had been evaluated by the EDQM, it would seem appropriate to reword condition 2. Moreover, if the related substances limits in the drug substance specification are widened to comply with the Ph.Eur monograph, it should be possible in these instances to also widen the limits for the corresponding impurities in the drug product specification without it being a Type II variation. A category in B.III.2 or B.II.d.1 should be included to cover this (common) scenario.	Reword Condition 2: 2. Unchanged (excluding tightening) additional (to Ph. Eur. **and CEP**) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.III.1	**Submission of a new or updated Ph. Eur. Certificate of suitability or deletion of Ph. Eur. certificate of suitability:** **For an active substance** **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient** Condition 11 11. If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.	Condition 11 states that a non-sterile API indented for use in a sterile finished dosage form must be claimed to be endotoxin free if water is used in the last step.	Amend to: 11. If the active substance is not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also ~~be claimed to be free from bacterial endotoxins~~ **meet an appropriate limit for bacterial endotoxins (e.g. corresponding to Ph. Eur.).**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.III.2	Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State Conditions 1. The change is made exclusively to fully comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests. 3. No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened	Condition 3 could contradict condition 1 in certain cases and this should be addressed to avoid confusion / incorrect invalidation of IA variations. Often impurity limits in a new Ph.Eur monograph are wider than those in the current specification as Ph.Eur monograph is based on data from a number of sources. In these cases one adopts the monograph completely (as per condition 1) the limits would be widened for related substances which could be seen as non-compliance with condition 3.	Clarification is required
B.III.2	Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State Documentation 5. A copy of the Ph.Eur. monograph /Member State national pharmacopoeia monograph for the concerned material as appropriate..	The request of a copy of an official pharmacopoeia seems unnecessary as all Health Authorities have access to the Ph.Eur or the member state pharmacopoeias. It would cause additional effort to provide these documents in the product dossier without giving any additional information in terms of product quality/safety information.	Remove Documentation 5

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.III.2	Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State Documentation 3. Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch.. For herbal medicinal products, comparative disintegration data may be acceptable.	The documentation for all 4 changes described in this paragraphs require the document no.3 – batch analysis data on API and in addition also, where appropriate, the dissolution data on the finished product (or disintegration for herbal product). Such change – changing the reference of the API from internal standards to EP or any other standards could not have the influence on the dissolution profile. The API itself remains unchanged, the manufacturing process itself is unchanged and no limits are being widened, only the reference (standard) is changed, therefore no influence on the finished product can be anticipated. Comparative dissolution profile should never be applicable.	Amend as follows: 3. Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification ~~and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch..~~ For herbal medicinal products, comparative disintegration data may be acceptable.
B.III.2	Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	This category should cover changes to remove internal method/method number and compliance with Ph. Eur.	Add **d) Removal of in-house method, method number to comply with the relevant monograph of the Ph. Eur.**

Variation number	Currently proposed or revised change	Comment	EGA proposal
B.IV.1	Change of a measuring or administration device **Condition** **6.** The proposed device presentation is not intended to be a solvent for the finished product.	Please give an example of a medical device being intended as a solvent for a finished product.	
C. Safety, Efficacy, Pharmacovigilance changes			
Variations which have not been listed in the proposed guideline but need to be covered			
	User testing of the leaflet/bridging report	There is a need for a separate category of variation to submit the results of the user testing of PIL or bridging report. This variation was clarified under Art 5 Procedure as Type IB and published in the CMDh table as C.I.z[1].	To add a variation (Type IB): *Submission of results of assessments carried out on target patient groups in order to comply with Article 59(3) of Directive 2001/83/EC and any resulting change to the Package Leaflet.*

[1] Heads of Medicines Agencies: Art 5 recommendations

Variation number	Currently proposed or revised change	Comment	EGA proposal
	Changes to PIL linked/ not linked to the SmPC. Some minor editorial changes.	A variation is needed to make minor editorial changes to PIL in line with SmPC. in addition, if the change to the PIL is not related to the SmPC, it should be submitted in accordance with art 61.3 Dir 2001/83 as amended, not as C.I.z. In view of several MS preferring the submission as C.I.z, a clear note/ new category is needed to avoid disharmony in procedural approach.	This should be added as a listed variation
	Submission of a Risk Management Plan (RMP) or changes to a RMP	There is no variation related to the Submission of a Risk Management Plan (RMP) or changes to a RMP listed in the guideline. Thus, we understand that the intention is to treat it as Type IB by default (we agree with IB as a category). However, in view of different approaches of Authorities already heard, it would be recommended listing this variation to avoid inconsistency and to increase the predictability of procedure. In view of risk related to the type of product, the distinction should be also made in case of the introduction of a RMP for a generic product (art 10.1) for which the originator is not executing risk management measures.	To introduce a separate category of variation (IB) to submit or to update the Risk Management Plan. It may be also an option to go for lower category of variation for generic products (for which the originator is not executing risk management measures).

Variation number	Currently proposed or revised change	Comment	EGA proposal
C.I.2.a **C.I.3.a**	C.I.2.a - Change in SmPC, Labelling or PL of generic/hybrid/biosimilar product following assessment of the same change for the reference product; No new additional changes C.I.3.a - Implementation of changes requested by the EMA/NCA; No new additional changes	CMD(h) QA-List for the submission of variations according to Commission Regulation (EC) 1234/2008 (CMDh/132/2009/Rev13) (Question 3.5, page 8) includes a recommendation to include a declaration that the proposed texts are identical to the reference text. This recommendation has not been addressed in the conditions / documentation of this variation category in the guideline. We would be happy to omit this administrative request; however it needs to be clear whether the lack of this document in the list of requested documents is a conscious decision of regulators (which we would be happy to support) or this document is simply missing in the guideline. If this document has been missed, it should be added to the list of required documents.	To agree with the Competent Authorities that a declaration that the proposed texts are identical to the reference text will be no longer requested. Or to add this declaration to the list of requested documents.

Variation number	Currently proposed or revised change	Comment	EGA proposal
C.I.8	Introduction or changes to a summary of pharmacovigilance system for medicinal products for human use a) Introduction of a summary of the pharmacovigilance system b) Changes in QPPV (including contact details) and/or changes in the PSMF location	Introduction of a **summary of the pharmacovigilance system** should not be made by a variation. The information which constitutes the summary of the PhV system is already in the possession of the Competent Authorities and does not need to be resubmitted under a new title. Even if the "super grouping" is used to simplify the procedure, the costs of such a change (if charged on MA basis) should not be multiplied by number of MAs grouped. Otherwise the costs for the industry are going to be extremely high. As it is in the guideline now, the estimated costs for such a bulk variation can be up to €7 mio for large companies, although the assessment will the same for one product or 20 000 products. Another option is to have reduced fees for this "only needed once" variation, or have a fixed fee for a MAH per a summary of the PhV system. It can save the authorities and the companies a lot of administrative burden and huge costs on industry's side. The same comments apply to changes of the QPPV/ PSMF location. Those changes shall not be charged per MA (even if grouped), but should be charged as a one assessment. This would provide a good interim solution until the Article 57 database is fully functional. A possibility to avoid future variations regarding QPPV contact data/ PSMF location by updating Art. 57 database (EVPRM) and referring to the current version of the PSMF is very much welcome by the industry as a pragmatic solution.	Introduction of a **summary of the pharmacovigilance system** should not be made by a variation; only further changes shall be reported as variations (with keeping in mind the availability of info in the EMA database (art 57).

Variation number	Currently proposed or revised change	Comment	EGA proposal
		For change a) the documentation to be supplied indicates 1, 2 and 3. We believe that it will aid clarity if the two asterisks are also added after the 3, i.e. 1, 2 and 3**, so that the reader will know documentation item 3 is only required once the EMA IT system is in place.	To add two asterisks after the 3, i.e. 1, 2 and 3**, so that the reader will know documentation item 3 is only required once the EMA IT system is in place.
C.I.9	Changes to an existing pharmacovigilance system as described in the DDPS	It has to be assured that not all changes of the DDPS does affect MAs. Only major changes related to QPPV name and contact details and other important information (as minimum as possible) are reported as Type IA or IA IN, all other changes should not have influence on MAs. It should be somehow taken for granted that for all MAs of one MAH, the last version of DDPS is valid.	

Variation number	Currently proposed or revised change	Comment	EGA proposal
C.I.10 Note	C.I.10 Changes to the conditions and/or obligations of the marketing authorisation due in particular to new quality, pre-clinical, clinical or pharmacovigilance data Note: This variation covers the situation where the only change introduced concerns the conditions and/or obligations of the marketing authorisation, including the conditions and/or obligations of marketing authorisations under exceptional circumstances and conditional marketing authorisation.	It is **not clear** what this section is actually covering? Which conditions/obligations - any kind, including those to provide real time stability data later on? Does it include the fulfilment of the obligations and the sending-in of the related documentation, or only if MAH is requesting a change of the still pending conditions/obligations? In addition what is meant with the "only" change? Does this mean that a change in conditions cannot be combined with other changes, or whether C.I.10 applies only if the change does not concern obligations listed in an RMP or else? Would this mean, that once the LoU is abolished and the commitments are included in Annex II, a Type II variation needs to be submitted each time the conditions and/or obligations are changed?	Clarification is needed

C.I.11	Change in the frequency and/or date of submission of periodic safety update reports (PSUR)	The note given in the end is of great help since it clarifies that a variation would be needed only for those products still requiring a PSUR submission, and which have a specified PSUR cycle mentioned in the MA approval letter. However, in case of some previously granted MAs, a specified PSUR cycle was explicitly mentioned in the MA for clarification purpose. In view of clarification provided by the EMA/ HMA in their document published in May 2012[2] stating that: *"For generic medicinal products authorised under the legal basis of Article 10(1) of Directive 2001/83/EC, standard statement referring to the PSUR cycle of the reference medicinal product may have previously been included in the MA for clarification purpose. In the context of the new pharmacovigilance legislation,* ***such standard wording on PSUR cycle should no longer be regarded as a condition to the MA, nor an obligation to submit routine PSURs as of 2 / 21 July 2012.*** *Such statement* ***will need to be removed****, as appropriate, following publication and aligned with the EURD list".* We understand that despite the standard sentence in the valid MA, the submission of the routine PSUR will not be required anymore *as of 2 / 21 July 2012*. The sentence that "*such statement will need to be removed*" stipulates a variation process. **We trust this is NOT the intention to impose another purely administrative variation** without any benefit for safety of patient. Companies will not submit any variation since the mandatory nature of the EURD list will override any current PSUR DLPs. There is a legal obligation for MAHs to follow the list and therefore there is no need to submit any variation. This needs to be clearly express or in the guideline or in the revised QA.	Clarification is needed

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C.I.11 Conditions	**Conditions:** The change in the frequency and/or date of submission of the PSUR has been agreed by the CHMP/CMDh, as set out in the list of Union reference dates.	Does C.I.11 apply to changes to the PSUR cycle already agreed with CHMP during other procedures such as renewal but different to the cycles stipulated in the list of union reference dates?	Clarification is needed
C.I.12	Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	This is a IAIN change implying that companies submit the notification immediately after 'implementation'. Industry's assumption is that the trigger for the submission in this case is the date of introduction of amended packaging by the company rather than the date the list of medicinal products that are subject to additional monitoring was updated. A clarifying note to this effect would be welcomed. It would not be possible to introduce new artwork 'immediately' after the list is updated; lead times for new packaging component introductions are usually a number of months.	To add clarification regarding the point of starting to count the "immediate implementation".

[2] European Medicines Agency - 2010 pharmacovigilance legislation - Questions and answers on implementation of pharmacovigilance legislation