EuropaBio comments on the public consultation paper on the review of the variations guidelines

EuropaBio, the European Association for bioindustries, welcomes the opportunity to comment on DG SANCO's review of the current EU Variation Categorisation guideline. EuropaBio's mission is to promote an innovative and dynamic biotechnology-based industry in Europe. EuropaBio has 68 corporate and 13 associate members operating worldwide, 2 Bioregions and 19 national biotechnology associations representing some 1800 small and medium-sized enterprises.

In general, EuropaBio supports the majority of proposals made by the Commission. However, we believe that there is an opportunity to maintain or even increase the level of public health protection by further simplifying the system, without compromising human health. A simplification of the system would allow industry to focus its human and fiscal resources on innovation and efficiency efforts for the development of high quality, safe and effective medicinal products. By reducing the unnecessary administrative burden on companies and maintaining a right balance between the protection of public health and support for innovation, such guideline could stimulate the introduction of changes that are beneficial to patients and society in general.

Please find below a list of general and specific comments on the public consultation paper.

We would welcome the opportunity of a meeting with the relevant officials within unit D5 of DG SANCO to further discuss our comments.

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EuropaBio's identification number in European Commission Register of interest representatives: **1298286943-59.**

1. General Comments

EuropaBio welcomes the majority of changes made to the current categorisation guideline, but would like to make some comments, which we will appreciate the European Commission to take into account when preparing the final update.

The Commission Public Consultation Paper (Oct 2007) on the Revision to the Variations Regulation introduced the concept of Design Space and acknowledged that continuous improvement of manufacture should be supported, '*e.g. by providing further flexibility to manufacturers who have undertaken the efforts to put in place modern quality tools'* (as described in ICH Q8(R2), Q9 and Q10). Whilst we recognise it might be challenging to introduce definitive guidance on this in the guideline, we believe that the Introduction should acknowledge that an 'enhanced Quality by Design approach' to pharmaceutical development provides opportunities for a more science and risk based approach to assessing changes for active substances and/or drug products than those developed by a 'minimal approach'.

Whilst the document introduces a number of QbD-related terms, these are not used consistently or appropriately across the document e.g. the term 'specification parameter' is used in section B.I.b.1 and B.II.c.1; 'parameter' seems to be referring to process parameters, and material attributes. Furthermore the term 'acknowledged enhanced development approach' is used throughout the guideline. This is not consistent with Q8 (R2). It is important that the appropriate QbD-related terms are used consistently and appropriately across the guideline, in order to avoid confusion and enable appropriate interpretation of the guideline.

We welcome the separation of 'Design Space' and 'Post-approval Change Management Protocol' variation categories. We also welcome the elaboration of the sections dealing with 'Post-approval Change Management Protocols'. However, we believe more flexibility could be introduced, by relaxing some of the Conditions for the Post-Approval Change Management Protocol changes, which would encourage their use.

We would also wish to highlight that the overall page numbers in the Table of Content is not aligned with later Sections.

Our comments in the "general comments" section are listed in chronological order, rather than by order of importance. Additional specific comments are listed in a separate section, in chronological order.

Relevant paragraph and variation number	Comment and rationale	Proposed change
B.I.a.1.j) (page 11)	**Comment:** Variation B.I.a.1.j related to a site of testing for biological methods upgraded to a Type II seems disproportionate. Such previous change was assigned to type IB (by default) category B.1.a.1.f as condition 2 (the active substance is not a biological/immunological substance or sterile) was not met. It is unclear what data would be needed to support this Type II variation as method transfer documents are generally considered GMP information subject to inspection and could still be submitted, if required, as part a Type 1B variation.	**Change:** New category B.1.a.1.j should be deleted and changes to a site of quality control testing using biological methods should be handled as a Type 1B (by default) category B.I.a.1(f) variation
B.I.a.1 k) (page 11) New storage site Master Cell Bank and/or Working Cell Banks	**Comment:** This item should be removed from this list, as it is a GMP issue.	**Change:** ~~***New storage site Master Cell Bank and/or Working Cell Banks***~~
B.I.a.2. c) (page 12)	**Comment:** The way the newly added text ***("…, which may have a significant impact on the quality, safety and efficacy…"***) has been incorporated makes the reading of the sub-category rather confusing and the overall objective is not totally clear. Does the added wording refer to both a	**Change:** Additional sub-category in B.1.a.2 ***"The change refers to the use of a different chemically derived substance in the manufacture of a biological/immunological substance which have no impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol"***.

	change to a biological/immunological substance and the use of a different chemically derived substance in the manufacture of a biological/immunological substance, or does it simply refer to the latter (i.e. “the use of a different chemically derived substance in the manufacture of a biological/immunological substance”)? If the added text refers to the latter only, then we can reasonably assume that it implies that for changes to chemically derived substances used in the manufacture of a biological/immunological substance and which have no significant impact on QSE on the finished product, these could be classified as “type IB by default”; which we certainly welcome. If that is the intent of this text modification, then we would recommend including an additional category which explicitly foresees a Type IB change where it is determined that there is no significant impact on the QSE, as this would help avoiding confusion and divergent interpretations.	*Procedure type: **IB***

B.I.a. 2. c) (page 12)	**Comment:** Given the length of the description of this sub-category, the wording *"and is not related to a protocol"* at the end may be confusing for the reader, and could potentially lead to divergent readings (i.e. the words *and is not related to a protocol may be understood as referring to (1) a* change to a biological/immunological substance or (2) the use of a different chemically derived substance in the manufacture of a biological/immunological substance, or to both (1) and (2). In addition, we believe it would add clarity if the guidance would specify that by "protocol" it refers to "post-approval change management protocol" (categories B.I.f)	**Change:** ***"Change not related to a protocol(*), and referring to either a*** *biological/immunological substance, or* ***to the*** *use of a different …"* ***+ (*) Footnote : "The term "protocol" refers to "Post-approval change management protocols" as foreseen in sub-categories B.I.f.1 to 4"***
B.I.a. 2 f) (page 13) – Active Substance 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) **B.I.a. 4 g) (page 15) – Active Substance):** Change to the limits of non critical processes parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing step(s).	**Comments covering below page 13, page 15, page 39 and page 43:** Non-CPPs are normally defined in the original MAA and changes to non-CPPs should be managed within a company's Pharmaceutical Quality System, which would be transparent at the time of an inspection. Implementing Q8/Q9/Q10 provides a Company with the opportunity of enabling continuous **improvement,** and a more science and risk based approach to managing changes with less regulatory oversight. Reporting changes to non-CPPs as Type IA variations would be	**Sections B.I.a.2 f) (pag 13);** ***~~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)~~*** **Section B.I.a.4 g) (page 15):** ***~~g) Change to the limits of non critical processes parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing step(s).~~***

B.II.b.3 g) (page 39) – Finished Product: Change to non critical processes parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing steps **B.II.b. 5. g) (page 43) – Finished Product:** 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)	contrary to this overall philosophy.	**B.II.b.3 g) (page 39):** ~~**g) 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).**~~
B.I.b.1. f) (page 18)	**Comment:** The text should specify that a Type II procedure should only apply when the change is expected to have a significant impact on the overall quality of the active substance and/or the finished product. This is foreseen under sub-category B.I.b.1 (g) and we suggest using the same language for sub-category (f).	**Change:** *"f) Change outside the approved specifications limits range for the active substance**, <u>which may have a significant effect on the overall quality of the active substance and/or the finished product</u>"***
B.I.f.4 d) (page 27) Implementation of a change for a biological/immunological medicinal product	**Comment:** The variation type implies that it concerns all changes for a biological/immunological medicinal product. However, biological/immunological medicinal products should also be able to use B.I.f.4.a) and b) if applicable and with reference to documentation to be supplied no. 2.	1) Add additional condition for sub-categories B.I.f.4.a, B.I.f.4.b – ***new Condition "2. <u>The protocol is not relating to a biological/immunological product</u>"*** 2) add additional text in brackets to the description of sub-category B.I.f.4.c ***: "… <u>(in a protocol not relating to a biological/immunological product)</u>"***

	For the sake of clarity and to avoid risks of confusion/misinterpretation, an additional condition should be added for sub-categories B.I.f.4.a and B.I.f.4.b.	
B. II. b. 2. c) 3. (page 38)	**Comment:** Variation B.II.b.2. c) 3. related to a site of testing for biological methods upgraded to a Type II is seems disproportionate. It is unclear what data would be needed to support this Type II variation as method transfer documents are generally considered GMP information subject to inspection and could still be submitted, if required, as part a Type 1B variation.	**Change:** New category B.II.b.2. c) 3. should be deleted and changes to a site of quality control testing using biological methods should be handled as a Type 1B (by default) category B.II.b.2(c)1 variation
B. II. b. 3. c) (page 39)	**Comment:** The current wording of B.II.b.3. c) *("The product is a biological/immunological medicinal product and the change requires an assessment of comparability"*), and foresees a Type II procedure. Our reading is that minor changes to manufacturing processes which do not require an assessment of comparability could be considered as Type IB by default. However, we believe that it would be clearer, would facilitate the reading of the guideline and would limit risks of misinterpretation if a specific sub-category for such minor changes	**Change:** 1) Reword the description of sub-category B.II.b.3. c) as follows: *"The product is a biological/immunological medicinal product and the change* ***may have a significant impact on quality, safety and efficacy and*** *requires an assessment of comparability"* - Procedure type : **II** 2) Add a further variation under B.II.b.3 for submission of minor variation to biological product manufacturing processes as follows: ***"The product is a biological/immunological medicinal product and the change does***

	would be added explicitly stating that a Type IB procedure applies.	***not require an assessment of comparability"*** **-** Procedure type: **IB**
B.II.d. 1. e) (page 50)	**Comment:** The text should specify that a Type II procedure should only apply when the change is expected to have a significant impact on the overall quality of the finished product. We suggest using similar language as for the active substance, sub-categories B.I.b.1 (f) and (g).	**Change:** *"e) Change outside the approved specifications limits range for the active substance***, *which may have a significant effect on the overall quality of the finished product"***
B.II.d.1. h) (page 50) Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product	**Comment:** We do not see the necessity for Type IA_{IN} notification. The usual implementation time of such changes is 6 months.	**Change:** *Type IA, **if implemented later than 6 months after update of the monograph***
B.II. d. 1. i) (page 50) 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)	**Comment:** Conditions 2, 3 and 4 are not proportionate requirements in our view. If new requirements are included in an updated monograph, with corresponding methods, these methods would be considered validated. If the requirement is new, a range will probably not exist; and limits most often will be directed by the monograph. Thus, additional assessment would not be required. A Type IB variation will therefore not be relevant.	**Change:** The procedure type for this element should be amended as follows: ***~~IB~~ IA_{IN}***
B. II. d. 1. j) (proposed new category) – (page 50)	**Comment:** We suggest adding a sub-category widening of the approved specifications limits to align	**Change:** New sub-category ***B.II.d.1(j): "Widening of the approved specifications limits, which***

	with what is foreseen for the active substance	***may have a significant effect on the overall quality of the finished product"*** - Procedure type : **II**
B. II. e. 1. b) – (page 53)	**Comment:** As reworded in the new Commission proposal, this sub-category seems now to imply that the addition of a new container for sterile medicinal products and biological/immunological medicinal products is now to be processed as a Type II variation (e.g. the addition of a glass pre-filled syringe container in addition to an existing glass vial presentation for a vaccine). Although we support the classification of such a change as a Type II procedure, this appears in contradiction with what is advised in the Commission Guideline on the categorisation of New Applications (NA) versus Variations Applications (V) (October 2003), where such a change is considered as a line extension.	**Change:** We welcome the proposed re-wording in the Commission variations classification guideline and would recommend updating the 2003 Guideline on the categorisation of New Applications (NA) versus Variations Applications (V) to reflect this.
B.II.e.5. a) 1+2 (page 57 and 58) Documentation 4)	**Comment:** The additional documentation number 4) seems to be a condition rather than a request for documentation to be supplied. Otherwise, the way in which this should be documented should be specified.	**Change:** Move the following to "Conditions", as new point 4: *4) In case of multipack/ bundle pack, the multipack/ bundle pack must ensure that the packs remain together during transportation and in pharmacy and should contain all legally required labelling items for the outer packaging, including blue-box (BB) information. In addition, it should comply with*

		the applicable guidance at EMA/CMD level.
B.I.f.2 (page 26) and B.II.h.2 (page 63)	**Comment:** There is no need to have a Condition applied to the deletion of a protocol. Whether or not there are unexpected events or OOS, the protocol could be deleted by Type IA***IN*. The Agency can always request more information after submission of the Type IA***IN*** if there are concerns regarding the proposed deletion. There is no risk to patient since the change will not be implemented in either case.	**Change:** Remove the Condition from this section.
B.I.f.3 (page 27) and B.II.h.3 (page 63)	**Comment:** The terms '*major*' and '*minor*' are subject to interpretation and should be avoided.	**Change:** (a) to be reworded as "***Changes to an approved post approval change management protocol that fundamentally change the content or approach of the protocol"*** (b) to be reworded as "***Changes to an approved post approval change management protocol that do not fundamentally change the content or approach of the protocol."*** Additionally, it is suggested to add the note regarding minor changes reflecting updated analytical tests and limits, which accompanies

		B.II.h.4, to this change as well.
B.I.f.3 (page 27) and B.II.h.3 (page 63)	**Comment:** The requirement for a '*declaration that assessment of comparability for biological products is not required'* is not clear. Most PACM Protocols for biological products will include an assessment of comparability, and the prospect to downgrade comparability assessments from Type II to Type IB is a primary driver behind the use of PACM Protocols for such changes.	**Change:** Remove the "*declaration that an assessment of comparability is not required"* from the Documentation for this change.
B.I.f.4 (page 27) and B.II.h.4 (page 63)	**Comment:** Please see above comment regarding "*declaration that an assessment of comparability is not required*." Same comment applies to this change.	**Change:** See B.II.h.3.
B.II.h.4. (page 63)	**Comment:** As the reporting category for a biological is B.II.h.4.d (Type IB), then we recommend that for the sake of clarity and to avoid risks of confusion/misinterpretation an additional condition should be added for sub-categories B.II.h.4.a and B.II.h.4.b.	**Change:** 1) Add additional condition for sub-categories B.II.h.4.a, B.II.h.4.b – new Condition ***"2. <u>The protocol is not relating to a biological/immunological product</u>"*** 2) add additional text in brackets to the description of sub-category B.II.h.4.c ***: "… <u>(in a protocol not relating to a biological/immunological product)</u>"***

B III.2: (page 69) Documentation, point 5	**Comment:** It should not be necessary to submit copies of the main pharmacopoeias Ph. Eur /BP/ USP.	**Change:** ***~~5. A copy of the Ph.Eur. monograph /Member State national pharmacopoeia monograph for the concerned material as appropriate.~~***
B.IV.1.Medical Device (page 71) Documentation, point 5		**Change:** Add item d) to: "Change of a measuring or administration device" ***d) Addition or replacement of a device which is an integrated part of the primary packaging:*** 5. Documentation: add: ***For an integrated drug-device combination the device part should follow the same requirements as for CE marking, i.e follow the essential requirements as well as quality systems requirements.***
B.V.c) (page 75) Change management protocol	**Comment:** A new section B.V.c) on "Change management protocol" was listed in the table of content on page 5, but there is no such section in the body of the document. The text goes directly from B.V.b) to C.	

2. Additional Specific Comments

Relevant paragraph and variation number	Comment and rationale	Proposed change
Annex (Table of Content) – **page 5**	**Comment:** The proposed table of content on page 5 should be amended as the current page references are not in line with the actual page numbers of the various sections.	
A.4 – page 7	**Comment:** The main text states *"…where no Ph.Eur. Certificate of Suitability is part of the approved dossier or a manufacturer of a novel excipient"*. This sentence requires clarification as it may be confusing for the reader who may wonder what to do in case of a change where a Ph.Eur. Certificate of Suitability was part of the approved dossier or in case of a change relating to a manufacturer of a novel excipient.	**Change:** Include a footnote to clarify this sentence. The footnote should make reference to later change categories (B.III.1 & B.II.c.5) for a manufacturer of a material/intermediate which requires a Ph.Eur.Certificate of Suitability or for a manufacturer of a novel excipient.
A.5 – page 8	**Comment:** Condition 1 requires clarification or rephrasing	**Change:** Condition 1. ***"All manufacturing operations shall remain the same for the specific site undergoing the name and/or address change"***
B.I.a.1 – page 10	**Comment:** The main text of variation category B.I.a.1 states *"…where no Ph.Eur Certificate of Suitability is part of the approved dossier".*	**Change:** Include a footnote to clarify this sentence. The footnote should make reference to relevant later change categories.

	This sentence requires clarification as it may be confusing for the reader who may wonder what to do in case of a change where a Ph.Eur. Certificate of Suitability was part of the approved dossier Clarification: does this mean if you have a Certificate of Suitability then this change category cannot be used? If not then delete this text and replace with proposed text below as these changes are covered in later change categories (see proposal to B.III.1)	
B.I.a.2. (Document 5) – page 14	**Comment:** Documentation item 5: new text has repeated word "that": *"5. Documentary evidence that that…."*	**Change:** ***"5. Documentary evidence that ~~that~~…."***
B.I.a.4 – page 15	**Comment:** It should be specified in the main text of this variation category that it also applies to intermediates if described in the dossier.	**Change:** *"B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance* ***or intermediates (if described in the dossier)****"*
B.I.a.4 (Document 5) – page 15	**Comment :** In the phrase *"… or a justification that they are obsolete."* (Documentation 5), it is unclear what the word "they" refers to: i.e. the risk assessment or the IP tests. We presume that it refers to the IP tests but it would be better to explicitly mention it to facilitate the reading.	**Change:** Documentation 5: "… or a justification that **the in-process tests** are obsolete."

B.I.b.1. h) – page 18	**Comment :** The text reads *"Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue"*. Due to the exclusion into brackets, it is not possible for manufacturers of biological or immunological substances to refer to this sub-category. However, when reading the whole text of category B.I.b.1 (including the conditions), the normal conclusion for the reader is that in the case of such a change for a biological or immunological substance the classification should be IB by default.	**Change:** Remove the parenthesis "…***~~(excluding biological or immunological substance)~~***…" or create an additional sub-category for biological/immunological substances
B. II. d. 1 – page 50	**Comment:** It should be specified in the main text of this variation category that it also applies to intermediates if described in the dossier.	**Change:** *"B.II.d.1 Change in the specification parameters and/or limits of the finished product* ***or intermediates (if described in the dossier)****"*
B. II. f. 1. c) – page 60	**Comment:** For some reason, there is no sub-category under B.II.f.1 covering changes in shelf-life for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol. We suggest covering this under sub-category (c).	**Change:** *"c) Change in storage conditions* ***or shelf-life*** *for biological medicinal products, …"*