# Submission of comments on the revision of Variation Guidelines

* Name of organisation or individual

EFPIA and VACCINES EUROPE

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If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below.

EFPIA/VE

**The stakeholder's consultation is launched on 13 June 2024 until 23 August 2024**.

Those participating in the external stakeholder's consultation are asked to consolidate their comments at their EU (Trade) industry association/organisation level, where applicable. The comments have to be submitted via the EU Survey tool, **by using the specific table below identified for each section of the Variations Guidelines (clean version)**. Please note that login is not required to fill in the survey.

## Comments on the guideline text

### 01. PROCEDURAL GUIDANCE ON THE HANDLING OF VARIATIONS

| | Line number(s) of the relevant text *(e.g. 20-23)* | Stakeholder name<br>*(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 6-7, 116, 176, 334-335, 385, 451-453, 629, 734, 759 | EFPIA/VE | Typographical/editorial corrections | Lines 6-7. Article 4(1) of the Variations Regulation charges the Commission with the task of drawing up and updating guidelines on the details of the various categories of variations, on the operation of …<br><br>Line 116. In case of extension(s) to the marketing authorisation supporting data relating to the proposed extension**,** Guidance on the appropriate additional studies…<br><br>Line 176. Notifications for minor variations of type IA […]<br><br>Lines 334-335. Proposed change: "...the reference Member State, the national competent authority, or the Agency (as appropriate)." |

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| | | | | Line 385. ....the EMA relevant Committee under Articles 32 to 34 of Directive 2001/83/EC)<br><br>Lines 451-453. Upon receipt of the opinion and the relevant information, the Commission will, where necessary, amend the marketing authorisation within 2 months in the cases laid down in Article 23(1a) of the Variations regulation.<br><br>Line 629. Included in the marketing authorisation will be issued by the Agency.<br><br>Line 734. "Within the evaluation period, the Agency may request supplementary…"<br><br>Line 759. For centrally authorised products, the Commission will, where necessary and provided that the necessary documents to amend the marketing authorisation(s) have been submitted, amend the relevant authorisation(s) within 2 months in the cases laid down in Article 23(1a) of the Variations regulation. |
| 2 | 23-26 | EFPIA/VE | This paragraph as written may be confusing. It is understood that the intent is that stakeholders should refer to the electronic version of these guidelines, updates included | The electronic version of these guidelines (insert link to electronic version) should be followed, together with any updates on the Commission website as well as any |

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| | | | on the Commission website, and any Article 5 recommendations. | recommendation issued in accordance with Article 5 of the Variations Regulation and not yet integrated. |
| 3 | 61-63 | EFPIA/VE | Article 61(3) notifications are intended to be simple and administrative procedures. We acknowledge that Directive 2001/83/EC allows for a 90-day procedure. However, both CMDh and EMA guidelines describe a shorter procedural timeframe. To enforce that this procedure is simple, we propose to not repeat the timeframe from the Directive which is understood to be a maximum timeline and per available agency guide should only be applied in exceptional cases. | In accordance with Article 61(3) of Directive 2001/83/EC, these changes are to be notified to the relevant competent authorities and they may be implemented if the competent authority has not objected. Normally a 20-day procedure applies (see EMA and CMDh websites). |
| 4 | 72 | EFPIA/VE | It would be helpful to specifically indicate that eCTD is the only format that is accepted. Also, the proposed edit improves the clarity of the sentence. | An application for variation shall be made electronically in eCTD format and must contain the elements listed in Annex IV to the Variations Regulation, presented as….. |
| 5 | 78-79 | EFPIA/VE | The EMA recommends the use of the PLM Portal web-based eAF for all CAPs variations starting from 14 May 2024 and to generate eAF on the PLM Portal. Suggested to recommend the new PLM portal eAF web-form that will replace the interactive PDFs for variations in the future and include a link. | The completed PLM portal electronic EU variation application form (eAF) (published under [insert link]), including the details... |
| 6 | 79-82 | EFPIA/VE | The date of implementation is only required in case of Type IA variations. For IB/II, applicants may include information that is not referring to a particular date. In addition, for MRP/DCP Type IB/II variations there will | …….. including the details of the marketing authorisation(s) concerned, a description of all individual variations submitted, information on their implementation and an indication that all conditions and documentation requirements |

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| | | | be different requirements regarding implementation in different Member States. | are met for type IA and IB variations, as applicable. |
| 7 | 82-84 | EFPIA/VE | It is not always possible to include all present and proposed information within the application form. It is also noted that in cases of worksharing procedures for national products the current text may not be completely aligned among the different member state. Therefore, a general description of all changes may be more appropriate. | A present and proposed table for all changes included in the submission should also be provided in the eAF or, where necessary, as an annex. |
| 8 | 92-97 | EFPIA/VE | Recommend revised wording to clarify the timelines for the provision of translations of the revised product information to reflect current practice. | For minor variations of type IA or IB the relevant translations should also be provided at submission whereas, in the remaining cases they should be provided in accordance with the translation timetable for the procedure for centrally authorised medicinal products or, respectively, within 7 calendar days after the end of the procedure for mutual recognition procedure and decentralised procedure. |
| 9 | 97-100 | EFPIA/VE | Wording does not reflect that for MRP/DCP submission of mock-ups or specimens needs to be made to CMS as well as RMS. | Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the variation, mock-ups or specimens should be provided to the reference Member States, the concerned Member States, the national competent authority, or the Agency, if applicable. |

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| 10 | 101-104 | EFPIA/VE | There can be cases of grouped variations in which the same supporting documentation is applicable for several categories. | For grouped variations concerning several marketing authorisations, a common cover letter and eAF should be submitted together with supportive documentation for each variation applied for and revised product information (if applicable) for each medicinal product concerned. |
| 11 | 107-109 | EFPIA/VE | In case of implementation of PSUSA outcomes or any other PRAC recommendations, the trigger is publicly available. It is a simplification and reduces administrative burden by mentioning the procedure reference in the cover letter, where applicable, instead of downloading public information and adding that to a submission to provide a copy. The documentation requirements for C.3 allow such a reference and do not request a copy. | For variations requested by the competent authority resulting from new data submitted, e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, the reference of the request should be provided in the cover letter or a copy of the request should be annexed to the cover letter, as appropriate. |
| 12 | 110-111 | EFPIA/VE | The inclusion of “complex” Type IB variations is a new, and in our view unnecessary concept that adds complexity to the classification of variations. It appears to be inconsistent with making lifecycle management more efficient and will require additional unnecessary work for regulators and industry compared with current Type IB variation requirements. Complex type IB variations do not exist in other jurisdictions and international alignment is critical to support the lifecycle management of a medicine and reduce risk of shortages. | With the exception of minor variations of Type IA and Type IB, an update or addendum to quality summaries, non-clinical overviews and clinical overviews as relevant. |

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| | | | We strongly oppose the new concept of "complex" Type IB variations and propose further discussion with stakeholders on this topic. | |
| 13 | 120-121 | EFPIA/VE | The addition of the link to the relevant EMA and CMDh webpages would be helpful and can be maintained through the regular review and updating (annually) of the classification guidelines. Furthermore, the possibility to contact the HA for advice on a particular upcoming variation through a pre-submission meeting, has been deleted. It is unclear if pre-submission meetings in the frame of a variation are not possible anymore or if related guidance in this regard should be available in another document/location (ie: currently EMA Q&A on post authorisation guidance only refers to written queries). In some circumstances, meeting discussions will be needed and helpful to facilitate the variation preparation and evaluation process. | Further details on technical requirements regarding the submission of variations applications are available on the EMA and CMDh websites [insert direct links]. Where appropriate, a pre-submission discussion may be organised with the reference Member State, the national competent authority or the Agency in order to obtain further regulatory and procedural advice. |
| 14 | 122-123 | EFPIA/VE | The requirement to provide any information related to the implementation of a given variation is unclear and worded so generally that it does not provide any helpful additional information. Specifically, the guideline should clarify whether this is a new requirement for Marketing Authorisation Holders to submit a follow-up submission related to implementation OR whether this | Proposed deletion of the following text: Any information related to the implementation of a given variation should be immediately provided by the holder upon the request of the relevant authority. |

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| | | | relates to existing expectations with regard to cGMP documentation and inspections.<br><br>It is recommended that these requirements and/or expectations remain within cGMP guidelines as opposed to being included as part of the amended variation guideline. | |
| 15 | 124-126 | EFPIA/VE | The proposed wording could be clarified to reflect different implementation timelines within a grouped variation. | It must be noticed that where a group of variations consists of different types of variations, the group must be submitted and will be handled according to the 'highest' variation type included in the group. If applicable, the variation type IA without immediate notification and which is not a consequential change of other changes included as part of the grouping, can be implemented at the declared implementation date without waiting for the outcome of the grouping variation. |
| 16 | 127-128 | EFPIA/VE | The concept of this proposal is welcome but the cases to which it may apply and the location of the information is unclear. Further clarification would be helpful. Possibly it would allow for certain related changes to be included within the scope of a single variation, e.g., changes to an analytical method used for both drug substance and drug product could be submitted under the scope of a single variation rather than submitting as separate variations for drug substance and drug product in a group? | Where justified, EMA and CMDh, as appropriate, may publish certain cases here [insert link] where related changes would be acceptable within a single variation application without categorizing the related changes as individual variations and grouping. |

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| | | | Adding a non-exhaustive list of acceptable cases as part of the guideline or in a central location would be helpful and prevent validation issues. | |
| 17 | 130-131 | EFPIA/VE | The following text has been deleted “Such minor variations do not require any prior approval, but must be notified by the holder within 12 months following implementation (‘Do and Tell’ procedure). However, certain minor variations of Type IA require immediate notification after implementation, in order to ensure the continuous supervision of the medicinal product.” Providing information that Type IA variations need to be implemented before submission is helpful guidance to retain. Also line 222 explains that IB variations are ‘Tell, Wait and Do’ procedures. We propose reinstatement of some text to bring consistency throughout the document. | Hereby guidance is provided on the application of Articles 7, 7a, 8, 11, 13a, 13d, 13e, 14, 17, 23 130 and 24 of the Variations Regulation to minor variations of Type IA. Such minor variations do not require any prior approval ('Do and Tell' procedure). |
| 18 | 139-141 | EFPIA/VE | The present wording does not include the RMS. Per lines 45/46 the term ‘concerned Member States’ only refers to CMS and not RMS. | However, at the latest within 12 months from the date of the implementation, a notification of the variation must be submitted simultaneously to all Member States concerned, to the national competent authority, or to the Agency (as appropriate). |
| 19 | 156-171 | EFPIA/VE | Per Article 1(9) of Commission Regulation (EU) 2024/1701, the new Article 7a of Regulation (EC) No 1234/2008 describes that the holder may submit a single notification of variations to the terms of more than one | Super-grouping may be applied where one or several Type IA (including Type IAIN) variations listed in all relevant chapters of the Annex to this guideline are notified at the same time for several marketing authorisations, regardless of |

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| | | | marketing authorisation referred to in Chapters II (MR/DCP), IIa (purely national) and III (centralised procedure) owned by the same holder where the same or several minor variations of type IA are notified at the same time and fall within one of the defined cases. We understand this article as meaning that MAH may group Type IA variations to products approved via any or all of the EU marketing authorisation routes into a single submission. The reasoning given for this revision was that practical experience and knowledge acquired from the worksharing procedure have shown that the grouping of variations could be extended to enable more flexibility and to increase harmonisation.<br><br>The proposed scenarios in the guideline do not provide the flexibility as intended by the legislation. The guideline is therefore missing an opportunity to simplify the handling of variations as intended.<br><br>In particular, it appears from the guideline that it is not permitted to super-group Type IA variations that affect products approved via both the centralised procedure and the purely national/mutual recognition/decentralised procedures. With current worksharing procedures, there is evidence and experience that procedures that include centralised marketing authorisations along with marketing | the route of marketing authorisation and the Member States concerned.<br><br>Proposed deletion of the following text:<br>- One or several Type IA variations listed in chapters A and B of the Annex to this guideline are notified at the same time for several marketing authorisations approved via the mutual recognition procedure and/or decentralised procedure and/or purely national procedure in several Member States.<br>- One or several Type IA variations are notified at the same time for several marketing authorisations approved via the mutual recognition procedure and/or decentralised procedure and the reference Member State is the same.<br>- One or several Type IA variations are notified at the same time for several marketing authorisations approved via the centralised procedure.<br>One or several Type IA variations are notified at the same time for several marketing authorisations approved via the mutual recognition procedure and/or decentralised procedure and/or purely national procedure in several Member States and the reference authority in consultation with the concerned |

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| | | | authorisations granted through other routes are running efficiently. Submissions for centralised licences should not be managed separately.<br><br>In addition, the current best practice guide already allows super-grouping variations for products with different RMS, in contrast to what appears to be permitted under lines 162-163. | authorities agree to the proposed super-grouping. |
| 20 | 181-183 | EFPIA/VE | The guideline is inconsistent with Regulation 1234/2008 as amended by Regulation 2024/1701, with regards to the requirements for grouping and annual reporting of Type IA variations. The guideline indicates that the relevant authorities' acceptance is required for grouping of Type IA variations for one MA only if not within the context of the annual update. Article 8(1) of the revised Variations Regulation, however, clearly indicates that Type IA notifications may be submitted as an annual update, or as part of a grouping or as part of a super grouping; authority acceptance is only required for immediate submission of Type IA variations not requiring immediate notification.<br><br>Requiring authorities' acceptance of grouping of Type IA variations outside the annual report reduces flexibility permitted in the revised regulation and will add to the complexity of handling variations, which goes against the goals of these revisions. | Proposed deletion of the following text:<br><br>Without acceptance from the relevant authorities, grouping of Type IA variations (not requiring immediate notification) for one marketing authorisation only (regardless of authorisation procedure) can only be used within the context of the annual update. |

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| 21 | 185-187 | EFPIA/VE | It is important to have only one common list of exceptional cases, which applies to CP, MRP/DCP and national approved products and sharing the location of such a list in this guideline will be helpful.<br><br>It should be noted that exceptional cases include dispensation to file Type IA variations as individual notifications where the change will ensure that the latest information is reflected in certificates of medicinal products (CPP), or circumstances where the change could have a supply impact.<br><br>For example, countries which require the EU licence or CPP as a reference may not have the legislative opportunity to file changes within 12 months after implementation. Not being able to file these individually to EU countries could lead to increased global supply chain complexity and could potentially lead to supply restrictions to global countries.<br><br>Further, it should always be possible to discuss and agree with RMS or EMA justified cases that are not (yet) published on the EMA/CMDh website.<br><br>This should not be limited to NCA (i.e. in accordance with the definition of NCA in chapter 1 the current wording reads as a discussion is only possible for purely national authorised products). | Individual notification of minor variations of type IA is acceptable in the cases listed on the EMA and CMDh websites [insert link], or in justified cases as notified to the Agency, RMS or national competent authority. |

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| 22 | 190-191 | EFPIA/VE | Include additional wording to state that the RMS or national competent authority will also acknowledge receipt of the variation submission (highlighting the specific change category and title). This is of utmost importance in the context of reliance on applications for Type IA variations by regulators worldwide. Furthermore, clarify that 30 days refers to 'calendar' and not working days. | The reference Member State or national competent authority, as applicable, will acknowledge receipt of a submission and review the Type IA notification within 30 calendar days following receipt. |
| 23 | 192-193 | EFPIA/VE | To support the use of reliance in non-European countries, the request is to specify that the Type IA variations do not require an assessment, despite this the letter should be considered as an endorsement of the submitted changes | By Day 30, the reference Member State or national competent authority, as applicable, will inform the holder and if applicable the concerned Member States of the outcome of its review, by specifying that minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder. |
| 24 | 193-198, 207-211, 281-283 and 315-316 | EFPIA/VE | (Same comment for lines 193-198, 207-211, 281-283 and 315-316, but not repeated due to limitations of commenting template.)<br><br>The guideline indicates that amendments to MA decisions will be made within 6 months (NAPs) or 12 months (CAPs) following Type IA variation notifications.<br><br>While recognising that this is in line with Articles 23(1)(b) and 23(1a)(b) of the Variations Regulation, the application of such a long timeline is of concern, particularly when taking into account the revised | No proposals for revisions to guideline text. EC, EMA and MS should consider ways in which decisions may be updated more rapidly when needed by MAH, and also how to educate or inform 3rd countries so that EU procedures do not result in delays in those countries. |

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| | | | requirement for annual reporting of Type IA variations.<br><br>Marketing authorisations in the EU and EU Member States are often used as reference authorisations in 3rd countries and updated EU/MS decisions following variations may be necessary to support approval of the concerned changes in those 3rd countries. Having a de facto delay of up to 18 months (NAPs) or 24 months (CAPs) between implementing a change in the EU and being allowed to implement the same change in 3rd countries raises significant planning and practical challenges to industry which could impact product supply in some cases. | |
| 25 | 201-202, 214-215 | EFPIA/VE | (Same comment for lines 201-202 and 214-215) but not repeated due to limitations of commenting template.<br><br>Use of “not implement" is inappropriate as prior implementation is a condition for IA submission. In addition, there can be cases in which rejection is received for administrative reasons. Such cases should not trigger an unjustified impact on supply. | If the variation is rejected for reasons that are not administrative in nature, the marketing authorisation holder must cease to apply the rejected variation(s), as applicable. |
| 26 | 202 | EFPIA/VE | The current version of the guideline states that *"failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation",* which is a positive element allowing to reduce the administrative burden related to resubmission and reprocessing of | …as applicable. Failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately upon the request of the relevant authority. |

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| | | | changes for minor administrative elements missing by mistake in the application. Keeping such flexibility will reduce administrative burden and mitigate unnecessary impact to supply, hence keeping this sentence in the guideline is recommended. | |
| 27 | 204-206 | EFPIA/VE | In addition to the Agency reviewing the Type IA notification within 30 days following receipt, it would be appreciated if the EMA would also acknowledge receipt of the variation notification (highlighting the specific change category and title). This is of utmost importance in the context of reliance application for type IA variations by regulators worldwide<br>Whilst we believe the EMA already does acknowledge receipt, it would be helpful if this was also reflected in the text of the guideline. | The Agency will acknowledge receipt of a submission and review the Type IA notification within 30 days following receipt, and a copy of the Type IA notification will be made available by the Agency to the rapporteur for information only. |
| 28 | 231-232 | EFPIA/VE | Wording does not reflect that for MRP/DCP submission needs to be made to CMS as well as RMS | or when this has been agreed previously with the Member State**s** concerned, the national competent, authority or the Agency (as appropriate). |
| 29 | 240-245, 343-348 | EFPIA/VE | (Same comment for lines 240-245 and 343-348, but not repeated due to limitations of commenting template).<br>We acknowledge that the revised Regulation makes use of the worksharing procedure mandatory in some cases. The guidelines should make it clear that such mandatory | Lines 240-245:<br>Furthermore, where the same minor variation of Type IB or the same group of minor variations (as explained above) affect several marketing authorisations owned by the same holder and are to be implemented at the same time, the holder must submit these variations |

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| | | | worksharing is only applicable when the same variation or group of variations is made to several marketing authorisations and is to be implemented at the same time for the concerned authorisations. There will be situations in which it is not possible, appropriate or necessary for the same change to be implemented for all affected authorisations at the same time. For example, the change(s) may be supply critical for certain products but not for others, or production cycles and schedules may be such that there will be differences in timing of implementation for different products. Further examples include the efficient management of labelling changes across multiple (numbering hundreds) of national licenses for various medicinal products. In such situations, and potentially others, the MAH must retain the flexibility to choose when and how to submit the variation for particular products.<br><br>In addition, competent authorities are most likely to be able to determine that marketing authorisations should be included in a worksharing application if the same changes have been submitted in parallel in separate variations. The possibility for authorities to request revision of a worksharing application should therefore be amended to reflect this. | as one application for 'worksharing' (see section 3 on 'worksharing'). The RMS, NCA or Agency may agree to exceptions to this requirement in justified cases. If the same change has been submitted in parallel in separate variations for affected marketing authorisations owned by the same holder, the holder will be informed and requested to revise its worksharing application.<br><br>Proposed deletion of the following text:<br><br>If a submission has been made as one or several variations but not including all affected marketing authorisations owned by the same holder in one application for 'worksharing', the holder will be informed and requested to revise its application.<br><br>Lines 343-348:<br><br>Furthermore, where the same major variation of Type II or the same group of variations (as explained above) affect several marketing authorisations owned by the same holder and are to be implemented at the same time, the holder must submit these variations as one application for 'worksharing' (see section 3 on 'worksharing'). The RMS, NCA or Agency may agree to exceptions to this requirement in justified cases. If the same change has been submitted in parallel in separate variations for |

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| | | | | affected marketing authorisations owned by the same holder, the holder will be informed and requested to revise its worksharing application.<br><br>Proposed deletion of the following text:<br><br>If a submission has been made as one or several variations but not including all affected marketing authorisations owned by the same holder in one application for 'worksharing', the holder will be informed and requested to revise its application. |
| 30 | 282-283 | EFPIA/VE | We propose addition of clarification on the implementation as per the CMDh Best Practice Guide for processing Type IB variations. | However, the accepted minor variations of Type IB may be implemented without awaiting the update of the marketing authorisation by the CMS, i.e. immediately after the RMS has informed the holder of its final acceptance. |
| 31 | 325-326 | EFPIA/VE | For alignment with similar provision on line 222. | Such major variations require approval by the relevant authorities before implementation. |
| 32 | 327-348 | EFPIA/VE | In accordance with current EMA Q&A on classification of variations (2.1), complex related changes such as changes of manufacturing sites coupled with a change in the manufacturing process to adapt to the new setting can be submitted under one single Type II variation.<br>It is proposed to add at the end of the section a general statement to provide the opportunity to report more systematically | Proposed text to be added after line 348:<br><br>Complex related changes (for example, a change of manufacturing site coupled with a change in manufacturing process, batch size and/or in-process limit; or a significant change in the manufacturing process coupled with a change in specifications) can be submitted under one single Type II variation. This variation |

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| | | | complex changes under a single Type II variation. This will contribute to make the lifecycle management of medicines more efficient.<br>Complex changes may also include changes in specification, which do not have to be submitted independently if they are due to the primary change (object of the Type II variation).<br>Notes can be added in the Annex to provide examples based on the Q&A. | should be classified based on the primary change triggering the other changes.<br>Complex related changes submitted under a single type II variation should always be clearly identified in the application form as follows: a clear description of all the related changes should be provided in the precise scope. All the related changes should be listed in the present/proposed table. |
| 33 | 353 | EFPIA/VE | The text is potentially confusing (in which cases would it not be applicable to submit an application to a concerned Member State?), so should be improved for clarity | If the application has been submitted simultaneously to the Member States concerned and contains the elements listed in Annex IV of the Variations Regulations and point 2., the competent authority will acknowledge receipt of a valid application of a major variation of Type II. The holder and the concerned Member States (when applicable) will be informed of the timetable at the start of the procedure. |
| 34 | 355 | EFPIA/VE | The inclusion of the text "....and point 2., the competent authority will acknowledge receipt of a valid application of a major variation of Type II" should be clarified so that it is clear that this relates to the National competent authority. | ..... and point 2., the National competent authority will acknowledge receipt of a valid application of a major variation of Type II. |
| 35 | 360-361 | EFPIA/VE | Information is missing for purely national procedures | .....them to the concerned Member States for comments as well as to the holder for information. In the purely national procedure, the competent authority will prepare a draft assessment report and a decision on the |

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| | | | | application according to the communicated timetable and will circulate them to the holder. The concerned Member States.... |
| 36 | 363-365 and 430-434 | EFPIA/VE | (Same comment for lines 363-365 and 431-434, but not repeated due to limitations of commenting template.)<br><br>For type II variations, timelines (including clock stop) are no longer stated (either for companies to provide supplementary information or for the agencies to assess the answers). We believe this information is helpful and important to enable streamlined assessment, efficiency of the procedures and predictability/reliability for continued supply of medicines.<br>We would therefore propose to reinstate the text from the current guideline related to these timelines. | Lines 363-365 (2.3.2. Type II variations assessment for mutual recognition and purely national procedures):<br>Within the evaluation period, the reference Member State or national competent authority, as applicable, may request the marketing authorisation holder to provide supplementary information, in which case the procedure will be suspended until the receipt of the supplementary information. The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period. In general, a suspension of 1 month will typically apply. For longer suspension the holder should send a justified request to the reference Member State for agreement.<br>The procedure will be suspended until the receipt of the supplementary information. The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.<br>After receipt of the holder's response, the reference Member State will finalise the draft assessment report and the decision on the application and will circulate them to the |

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| | | | | concerned Member States for comments as well as to the holder for information.<br><br>Lines 431-434 (2.3.5. Type II variations assessment for centralised procedure):<br><br>The evaluation will be suspended until the receipt of the supplementary information. In general, a suspension of up to 1 month will typically apply. For suspension longer than 1 month the holder should send a justified request to the Agency for agreement by the corresponding Committee. For any follow-on request for supplementary information, an additional procedural suspension of up to 1 month will be applied in general; a maximum of 2 months may be applied when justified.<br><br>The Committee assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data to be requested to the marketing authorisation holder. |
| 37 | 374-375, 377, 395 | EFPIA/VE | Clarify that it is the concerned Member State rather than Member State.<br><br>General comment: Throughout document where Member State is referenced, ensure that it clarifies concerned. | prevents a concerned Member State from recognising the decision of the reference Member State. The concerned Member State that, .... |

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| 38 | 395-405 | EFPIA/VE | Propose to change the order of text to better reflect the sequence of activities in the national phase of a type II variation and clarify timeline to define as 2 calendar months for amendment of marketing authorisation. | The accepted major variation(s) of Type II can be implemented 30 days after the holder has been informed about the acceptance of the variation(s) by the reference Member State, provided that the necessary documents to amend the marketing authorisation have been submitted to the Member State concerned.<br><br>After approval of the variation(s), the competent authorities of the Member States concerned will, where necessary, amend the marketing authorisation to reflect the variation(s) within 2 calendar months, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned.<br><br>In those cases where the application has been the object of a referral, the variation(s) must not be implemented until the referral procedure has concluded that the variation(s) is accepted. However, the variations in the group not subject to the referral may be implemented if so indicated by the reference Member State. |
| 39 | 427-428 | EFPIA/VE | Propose to add the timeline for the validation step of a type II to the sentence if it is not detailed elsewhere in this guideline?<br><br>"(…) the Agency will acknowledge receipt of a valid application of a major variation of Type II." | "(…) the Agency will acknowledge receipt of a valid application of a major variation of Type II within the timeline defined on the EMA website. |

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| 40 | 430 | EFPIA/VE | This text should be retained for the purposes of clarity, as there are a number of committees within the EMA. The simplification of the EMA structure is only expected at a later stage once the general pharmaceutical legislation has been revised. | Within the evaluation period, the Committee for Medicinal Products for Human Use may request supplementary information. |
| 41 | 437 | EFPIA/VE | Clarify “within 15 days” as calendar days<br><br>Include a general note that throughout the document, the number of days refers to calendar days | “15 calendar days” |
| 42 | 463-464 | EFPIA/VE | Sentences regarding implementation of safety issues has been deleted in section 2.3.3 (MRP) and 2.3.4 (NP). Propose to also delete this sentence here for centralized procedures. This would also address the point that there is no mention of a "grace period" for implementation after a variation is approved for changes that are NOT due to safety issues. | Proposed deletion of the following text: Variations related to safety issues must be implemented without delay, within a time-frame agreed between the Commission and the holder. |
| 43 | 596-598 | EFPIA/VE | For clarity, text should mention MRP/DCP as well | Urgent safety restrictions may also be imposed by the Commission (for centrally authorised medicinal products) or by the national competent authorities (for nationally authorised medicinal products, including those registered via mutual recognition and decentralised procedures) in the event of a risk to public health in the case of medicinal products for human use. |

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| 44 | 605-606 | EFPIA/VE | The statement ''in case of the completion of a paediatric investigation plan and the inclusion of the results of the studies in the product information:'' added at the end of the first paragraph, could potentially be misleading in the sense that it could be understood that these are the 2 only conditions to benefit from the reward (rather than being the conditions to receive the compliance statement.<br><br>There is also a typographical error at the end of line 606 which requires the deletion of a colon. | Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use (10) ('Paediatric Regulation') provides for rewards upon receipt of the statement of compliance, following the completion of a paediatric investigation plan and the inclusion of the results of the studies in the product information. |
| 45 | 621-622 | EFPIA/VE | Introduction of the term 'ad hoc' variation is confusing and should be clarified. Propose to streamline the wording and correct a typographical error. | Specifically, the compliance statement should be included in the context of a variation (e.g. submission of the results of PIP studies following PIP completion or as a standalone variation) to the relevant authority. |
| 46 | 631-635 | EFPIA/VE | The list of situations in which worksharing may be applied is unnecessary and confusing. We propose simplification of the text. | In accordance with Article 20 of the Variations Regulation a holder is required to submit in one application the same Type IB, the same Type II variation, or the same group of variations corresponding to one of the cases listed in Annex III of the Regulation or agreed with the reference Member State, the national competent authority or the Agency (as appropriate) which does not contain any extension affecting more than one marketing authorisation of the same holder, regardless of the route of registration. |

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| | | | | Proposed deletion of the following text:<br><br>(i) more than one purely national marketing authorisation of the same holder in more than one Member State; or<br><br>(ii) more than one mutual recognition marketing authorisation of the same holder; or<br><br>(iii) more than one centralised marketing authorisation of the same holder; or<br><br>(iv) one or several purely national marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder; or<br><br>(v) one or several purely national marketing authorisation(s) and one or several mutual recognition marketing authorisation(s) of the same holder; or<br><br>(vi) one or several mutual recognition marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder; or<br><br>(vii) one or several purely national marketing authorisation(s), one or several mutual recognition marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder. |
| 47 | 644 | EFPIA/VE | Retain the deleted guidance, as we understand that the pre-submission | .....variation on behalf of the other concerned authorities. In order to facilitate the planning of |

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| | | | activities (e.g. letter of intent) are still applicable. | the procedure, holders are encouraged to inform the Agency or the coordination group and the proposed reference authority in advance of the submission of a variation or group of variations to be subject to a worksharing procedure. |
| 48 | 695-697 | EFPIA/VE | For worksharing procedures not containing CP products, the option to approve the acceptable variations for some (but not all) products has been removed. This is still an opportunity for CP-containing worksharing groups. Please align – given worksharing is now mandated, products in which the change is acceptable should not be delayed / refused pending products for which the given change is currently not accepted / supported. | Proposed deletion of the following text:<br><br>In case of a favourable opinion, the list of variations that are not considered approvable should be attached in the Opinion (if applicable). In case of an unfavourable outcome, the grounds for the unfavourable outcome should be explained.<br><br>Replacement with the following text:<br><br>If the Agency considers that some variations are not approvable, the list of variations that are not considered approvable should be attached in the Opinion. Variations may be considered approvable for some of the concerned products only. |
| 49 | 698-701 | EFPIA/VE | There are instances during worksharing procedures (national licenses) when Members States taking more than 30 days to issue local approvals is causing complexities for implementation. Propose to replace 'will' with "must" in line 698. This is consistent with the approach in section 3.5 (line 752) which refers to the following "For medicinal products authorised under the mutual recognition procedure or decentralised or | When applicable, the concerned Member States must recognise the opinion within 30 days following receipt of the opinion and inform the reference authority accordingly, unless a potential serious risk to public health is identified that prevents a Member State from recognising the opinion of the reference authority. The Member State that identifies, within 30 days following receipt of the opinion of the reference authority, such a potential |

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| | | | purely national procedures, the Member States concerned must approve the opinion, and, where necessary, amend the national marketing authorisations within 60 days provided that the necessary documents to amend the marketing authorisation(s) have been submitted".<br><br>Furthermore, for clarity, some rewording to line 701 is proposed. | serious risk should inform the reference authority and give a detailed statement of the reasons for its position. |
| 50 | 711 | EFPIA/VE | Propose retaining the deleted guidance, as it is useful. Refer to calendar days for consistency. | ....Directive 2001/83/EC. After a positive opinion is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the holder should submit, within 7 calendar days, translations of the product information texts to all Member States concerned. |
| 51 | 735-737 | EFPIA/VE | Deleted text should be retained for the purposes of clarity, as there are a number of committees within the EMA. The simplification of the EMA structure is only expected at a later stage. | An oral explanation to the Committee for Medicinal Products for Human Use can be held at the request of the Committee or the marketing authorisation holder, where appropriate. |
| 52 | 805-808<br>(Section 4. Annex)<br><br>+<br><br>948-951 (introduction to Annex, section C) | EFPIA/VE | It is possible that a change affecting the therapeutic indication (or posology/maximum daily dose) may not trigger any change affecting the quality of the product.<br><br>As currently worded it is also not clear what justification would be needed. E.g., if the expectation is a statement signed by quality confirming that the proposed changes have | In case of a change in therapeutic indication, posology or maximum daily dose, a review of quality documentation may be performed (e.g. the need to change impurity limits or warnings for excipients with known effect/ threshold). If the change has an impact on the quality documentation the holder must submit the corresponding updated sections of the dossier as requested in the Annex for the given change. |

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| | | | no impact then this could also be part of the update/addendum to the clinical overview? | |
| 53 | 793-797 | EFPIA/VE | Reference to 'test procedure' having the same meaning as 'analytical procedure' can be removed because the term 'analytical procedure' is now consistently used in the Annexes. Similarly, for 'specification parameter' which has been replaced by 'specification attribute'<br><br>In addition, ensure that all occurrences of 'test procedure' and 'specification parameter' are replaced by 'analytical procedure' and 'specification attribute' respectively (see for example in lines 795 and 796, as well as in the Annexes) | For the purpose of this Annex 'limits' has the same meaning as 'acceptance criteria'. 'Specification attribute' means the quality attribute for which an analytical procedure and limits are set, e.g. assay, identity, water content. The addition or deletion of a specification attribute therefore includes its corresponding analytical method and limits. |
| 54 | 818/909/935 | EFPIA/VE | References in the Annex to monographs of the Ph. Eur. are only applicable to active substance and/or excipient monographs and/or general monographs, i.e. finished product monographs are exempted. Updates to 909 and 935 mean that it is not clear if there is an update to the monograph that impacts on finished product specification. | Require clarification why DP monographs are exempted. Footnote to be included in 909 or 935 with explanation on how to handle this point. |
| 55 | 113-114 | EFPIA/VE | The requirement for clinical Type II variations with a single CDR to provide information in sections 2.7.3 and 2.7.4 duplicates data summarized in section 2.5. The 2.5 Clinical Overview provides a comprehensive summary of the safety and efficacy findings | It is proposed to revise the guideline to allow for procedural flexibility where applicants may omit sections 2.7.3 and 2.7.4 for single CST clinical Type II variation applications, provided that the summary of safety and efficacy is |

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| | | | from the clinical study, making the 2.7 summaries redundant. A well-documented summary in section 2.5 ensures clarity and coherence in the presented data. Eliminating the requirement for sections 2.7.3 and 2.7.4 for single CSR Type II clinical variation applications would streamline the submission process. This reduction in redundancy will save time and resources for both the applicants and the regulatory authorities. | adequately presented in the 2.5 Clinical Overview. |

**02. ANNEX**

**A. ADMINISTRATIVE CHANGES**

| | Please insert reference to relevant scope or section *(e.g. A.1, A.2, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 854<br>A.2 | EFPIA/VE | The title of category A.2 is unclear regarding the term “medical device (part)”. This could be amended so that it is clear that it also includes integral medical devices. | Suggest revising the proposed title for A.2 as follows: Change in name of the active substance, excipient, medical device (including integral (device (part)), or packaging component. |
| 2 | 854<br>A.2 | EFPIA/VE | The EMA Q&A guidance for devices indicates that a justification as to why there is no | Amendment of the relevant section(s) of the dossier, including (if applicable), justification that there is no impact. |

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| | | | impact for a change in name should be included.<br><br>Change proposed to Documentation point (3), although could also go into point (2). | |
| 3 | 856<br>A.4 | EFPIA/VE | Clarification is required for the term “medical device (part)”. If also medical device part of an integral medical device is meant, it should be specified accordingly.<br><br>In addition, the term “supplier” is ambiguous, because it could also refer to a distributor, but mainly relevant should be the manufacturer.<br><br>Clarify where “(when mentioned in the dossier)” is applicable. Assume it applies only to “supplier of a packaging component, medical device (part), starting material, reagent and/or excipient”? Proposed amendment reflects this more accurately. | A.4 Change in the name and/or address of the marketing authorisation holder, ASMF holder, manufacturing site for an active substance, intermediate or finished product, primary and/or secondary packaging site, manufacturer responsible for batch release, site where quality control takes place, and/or the following where mentioned in the dossier: supplier of a packaging component, medical device manufacturer (including integral device (part)), starting material, reagent and/or excipient [Delete: (when mentioned in the dossier)] |
| 4 | 856 A.4 | EFPIA/VE | The variation categories for this change do not contain all variation types listed in the chapter title and therefore, it is unclear what the conditions or documentation requirements are for the full range of changes.<br><br>Further, the proposed categories are not relevant for medical devices. To provide clarity for applicants we suggest to include an additional category d only for devices.<br><br>We propose that this new category (d) would only require updated sections of the dossier (documentation 2). In case formal | a) The change in the name and/or address concerns the marketing authorisation holder or ASMF holder<br><br>b) The change in the name and/or address concerns a manufacturer(s) for an active substance, intermediate or finished product, primary and/or secondary packaging site whose activities include batch release<br><br>c) The change in the name and/or address does not concern a manufacturer(s) for an active substance, intermediate or finished product, primary and/or secondary packaging site whose activities include |

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| | | | documentation of relevant official body (1) is required, this would be the CE certificate which is supervised by the Notified Body (other documents listed in the draft guideline would not be relevant for medical devices). Please see proposal for updates to documentation (2) | batch release nor the marketing authorisation holder<br><br>d) Change in the name and/or address of a manufacturer of a medical device (including integral device (part)), when mentioned in the dossier." (procedure type 1A)<br><br>e) The change in the name and/or address concerns a site where quality control takes place,<br><br>f) The change in the name and/or address concerns a supplier of a packaging component, starting material, reagent and/or excipient (when mentioned in the dossier)<br><br>Documentation 2 Amendment of the relevant section(s) of the dossier, including revised product information as appropriate. For a medical device (including integral device (part), provide a revised CE certification or Declaration of Conformity, or a revised NBOp or justification for its absence, as applicable. |
| 5 | 856 A.4 and 857 A.5 | EFPIA/VE | Clarify that suppliers of packaging components and excipient (when mentioned in the dossier) should not require maintenance through submission of IA variations if the change does not impact the Quality of the product. This information can be regarded as supportive and managed in Company's PQS (Pharmaceutical Quality System) based on a risk assessment. The relevant sections can be updated at next | Include additional footnote for table A.4 and table A.5 specifying "Suppliers of packaging components and excipient (when mentioned in the dossier) should not require maintenance through submission of IA variations if the change does not impact the Quality of the product." |

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| | | | occasion to avoid unnecessary challenges to supply continuity in EU and reliant markets. | |
| 6 | 856 A.4 | EFPIA/VE | Accept direct database updates to PMS (part of SPOR) without the need for dossier submission for administrative Type 1A variations.<br><br>The successful precedence created by article 57 database for PSMF location and QPPV contact details change in the current system should be extended to other pure administrative changes having no impact on quality, efficacy and safety. The variation guideline should provide the option to use the SPOR database, and this should be reflected with an asterix and a footnote as proposed. | Add the following footnote:<br><br>This variation covers […]. Once the PMS database is functional, changes to […] may be updated through the PMS database only (without the need for a variation). |
| 7 | 857 A.5 | EFPIA/VE | Referring to condition (2) under A.5. "The deletion should not be due to critical deficiencies concerning manufacturing." We propose that this condition should be deleted. An MAH holder should be able to remove a manufacturing site that is not performing up to expectations without approval. | Proposed deletion of the following text (condition 2): The deletion should not be due to critical deficiencies concerning manufacturing. |
| 8 | 857 A.5 | EFPIA/VE | Clarification is required for the term "medical device (part)". If also medical device part of an integral medical device is meant, it should be specified accordingly.<br><br>In addition, the term "supplier" is ambiguous, because it could also refer to a distributor, but mainly relevant should be the manufacturer. | A.5 Deletion of manufacturing sites for an active substance, intermediate or finished product, primary and/or secondary packaging site, manufacturer responsible for batch release, site where quality control takes place, and/or manufacturer of a packaging component, medical device (including integral (device (part)), starting |

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| | | | | material, reagent and/or excipient (when mentioned in the dossier) |
| 9 | 857 A.5 | EFPIA/VE | Add the following note at the end of the section, in accordance with EMA Q&A on classification of variations 1.2. | Several manufacturing sites, manufacturers or suppliers can be deleted under a single variation under the classification A.5. It has to be assured that there is still one approved manufacturing site, manufacturer or supplier left in the documentation performing the same function as the one(s) concerned by the deletion. |

**B. QUALITY CHANGES**

**B.I Active Substance**

***B.I.a) Manufacture***

| | Please insert reference to relevant scope or section *(e.g. B.I.a.1.a, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | General comment | EFPIA/VE | There are several change categories where risk-based approach principles are not considered. For many of the changes related to manufacturing and testing of DS and DP the following condition is mentioned “The active substance/finished product is not a biological substance or sterile”. It is recommended to revise this condition, considering risk-based | Review all categories and conditions that have higher requirements for biologicals. Risk-based approaches should be considered (i.e., impact on Safety, quality, identity, purity and potency).<br>E.g., Condition:<br>[Replace: “The active substance/finished product is not a biological substance or sterile”] by ... “the change is not expected to have an impact on the |

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| | | | approach and scientific knowledge considering the impact on Critical process parameters & or Critical quality attributes (i.e. impact on Safety, quality, identity, purity and potency) of the medicinal product instead of whether the product is biological or not.<br><br>Similarly, some variation categories are specific to Biological immunological medicinal products with higher reporting category for these changes regardless of the impact on the overall quality of the product which is not aligned with the risk based approach principle (e.g. B.I.a.1 "d", "i"; B.I.a.3 "c"; B.I.b.2 "c", "g"; B.II.b.4 "c"; B.II.d.2 "c" | safety, efficacy, quality, identity, purity and/or potency of the final product." |
| 2 | General comment impacting B.I.a.1, Documentation 4, B.I.a.2 Documentation 2 and B.I.a.3 Documentation 2 | EFPIA/VE | B.I.a.1, Documentation 4, B.I.a.2 Documentation 2 and B.I.a.3 Documentation 2: Continued restrictive requirements for Biologicals versus small molecules. There should not be a general requirement to provide more comparative batch analysis data for biologics compared to small molecules.<br>It should be based on a risk assessment. In all cases, there should also be an option to provide data on at least two batches, unless otherwise justified. Rewording proposed for each case.<br><br>In addition, B.I.a.1 Documentation requirement 4 states that the comparative results of two batches of active substance be provided which is inconsistent with the specifics of the change. Changes in starting material suppliers have been successfully submitted justified using batch | B.I.a.1 Documentation 4:<br>Batch analysis data (in a comparative tabular format) for at least two batches, unless otherwise justified (minimum pilot scale) [Delete: or 3 batches (unless otherwise justified) for biologicals] of the starting material/ reagent/intermediate/active substance from the current and proposed manufacturers/sites.<br><br>B.I.a.2 Documentation 2:<br>Batch analysis data (in comparative tabular format) of at least two representative batches, unless otherwise justified (minimum pilot scale), [Delete: or 3 batches (unless otherwise justified) for biologicals] manufactured according to the currently approved and proposed process.<br><br>B.I.a.3 Documentation 2: |

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| | | | analysis data from two batches of the starting material on several occasions. For introduction of a site responsible for manufacturing of a starting material or an isolated intermediate, where impurity profile equivalence can be demonstrated at the starting material/intermediate, the active substance's impurity profile can be considered to be unaffected by the change in starting material/intermediate manufacturer. In that case, batch analysis data from the starting material/intermediate should be acceptable to support the addition or replacement of a site responsible for manufacturing a starting material or intermediate. Proposal to reword Documentation 4 to support starting material/reagents/intermediates manufacturer addition. | Batch analysis data (in a comparative tabulated format) on a minimum of two production batches (unless otherwise justified) of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. [Delete: Batch analysis data of 3 batches (unless otherwise justified) for biological active substance, should be available for the proposed batch size.] |
| 3 | 863<br>B.I.a.1 | EFPIA/VE | It is perceived that the deletion of the wording 'when no Ph.Eur. certificate of Suitability is part of the approved dossier' brings confusion.<br>First, it is not expected to file a B.I.a.1 variation in case of change of a manufacturer for an active substance under a CEP: a variation B.III.1.a)1 is expected (New CEP).<br>Second, for an active substance covered by a CEP it is not expected to submit individual variations related to change in manufacturer of starting material or intermediate. | Reinstall wording related to CEP:<br>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. |
| 4 | 863<br>B.I.a.1 | EFPIA/VE | <u>Condition 1:</u> Should be amended to remove reference to reagents (as they are not listed in the variation type any more) and for starting | <u>Condition 1:</u><br>For starting materials [Delete: and reagents] the specifications [Delete: (including in process |

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| | Condition 1 and Documentation 2 | | materials it should not be a requirement to have the same IPCs, as this detail is not typically part of module 3, i.e. the same specifications are a sufficient condition on their own. Also, many processes are designed to be scale independent such that changes in scale can be justified. Change in batch size is already covered in B.I.a.3. Rewording for condition is proposed.<br><br>Documentation 2: Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or "confirmation" in the submission should be appropriate. In addition, for consistency with condition 1, confirmation should only be required to state that specifications for starting materials and reagents are the same as those already approved. | 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 [Delete: (including batch size)] and detailed route of synthesis are identical to those already approved.<br><br>Documentation 2:<br>A [Delete: declaration] confirmation from the marketing authorisation holder (and the ASMF holder, where applicable) that the synthetic route, quality control procedures and specifications of the intermediate and active substance and specifications of the starting material/reagent [Delete: /intermediate] in the manufacturing process of the active substance are the same as those already approved. |
| 5 | 863<br>B.I.a.1.c, Condition 2, Documentation 5 and Documentation 6 | EFPIA/VE | B.I.a.1.c: Reagent is missing. Add clarification that when included in the dossier.<br><br>Condition 2: Prevents this change from being used in the context of synthetic starting materials used in biological or immunological products e.g., ADCs. The intention behind the restriction to ensure adequate control over biological starting materials is covered by new change B.I.a.1.d. Therefore, remove condition 2. | B.I.a.1.c:<br>c) Addition or replacement of a site responsible for manufacturing of a starting material/reagent (when included in the dossier) used in the manufacture of the active substance.<br><br>[Delete: Condition 2:<br>The active substance is not a biological substance or sterile.]<br><br>Documentation 5: |

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| | | | Documentation 5: For the addition or replacement of a site responsible for manufacturing of a starting material used in the manufacture of the active substance a QP declaration should not be required.<br><br>Documentation 6: Requests for a declaration from the Active Substance manufacturer committing to update the MAH on changes to drug substance manufacturing process is not relevant when adding a starting material supplier. Therefore, delete documentation 6. | [Delete: A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1.]<br><br>Documentation 6:<br>[Delete: Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and analytical procedures of the active substance.] |
| 6 | 863<br>B.I.a.1.b and B.I.a.1.d | EFPIA/VE | Addition or replacement of a site responsible for manufacturing of a biological active substance or a biological starting material should not be by default a Type II. Applicants should be able to utilise risk-based approaches as per ICH and file via Type IB when there is no significant impact on the quality, safety or efficacy of the medicinal product. A new condition 8 is proposed.<br><br>The sub-bullet for the addition or replacement of a site responsible for manufacturing of a | B.I.a.1.b and B.I.a.1.d:<br>[Replace: Procedure type II] by: Procedure Type IB. Add new condition 8: “There is no impact on the quality, safety or efficacy of the medicinal product. In case of any expected significant impact on the quality, safety or efficacy of the medicinal product, the change should be upgraded to Type II.”<br><br>B.I.a.1.d:<br>Addition or replacement of a site responsible for manufacturing of<br>-a biological active substance or |

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| | | | material for which an assessment is required of viral safety and/or TSE risk should either have a stand-alone section or also be categorized as a Type 1b variation based on a science- and risk-based approach provided that there is no impact on the safety or quality of the product. Therefore, the new proposed added “Condition 8” also applies. This new condition should apply to both, B.I.a.1.b and B.I.a.1.d.<br><br>Related changes concerning the manufacturing process or IPC can be submitted under this single variation. Therefore, proposal to add a note. | -a biological starting material /reagent/intermediate used in the manufacture of a biological active substance [Delete: which may have a significant impact on the quality, safety or efficacy of the medicinal product or<br>-a material for which an assessment is required of viral safety and/or TSE risk]<br><br><u>Note</u>:<br>Related changes required to adapt to the new settings of the manufacturing site, such as changes in manufacturing process, batch size, or in-process controls can be submitted under this single variation. All changes should be identified in the application form. |
| 7 | 863<br>B.I.a.1<br>Line before (i), B.I.a.1.i and B.I.a.1.j | EFPIA/VE | <u>Reword line before (i):</u> The post approval variation guideline does cover the changes in API stability study site. A few change types are currently available in the manufacturing section B.I.a.1 and they only talk about changes to the manufacturer, including quality control site. It is not very clear whether the API stability study site is also implicitly covered. Proposal to add clarification in line before (i). The quality control testing sites for starting materials has not been required previously and should be deleted.<br><br><u>B.I.a.1.i:</u> Clarify that testing could be release and stability to allow clarity that in-process testing are out of scope.<br>It is recommended to modify the text for this variation type for clarity i.e., Biologicals. Note: In some cases active substance (inclusive of | <u>Line before (i)</u><br>“Quality control testing (release and stability; in-process testing is out of scope) arrangements for the active substance [Delete: or starting material] or intermediate.”<br><br><u>B.I.a.1.i</u><br>Addition or replacement of a site where batch control/ release and stability testing of the biological active substance [Delete: or starting material] or intermediate takes place, applying a biological/immunological/immunochemical analytical procedure [Delete: for a biological active substance] (without change to the analytical procedures).<br><br><u>B.I.a.1.j</u> |

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| | | | biologics) is used in the changes but in some others biologics is spelt out – Propose that in the title of the change where active substance is mentioned it states inclusive of biologics (applies across all sections). Addition or replacement of quality control testing arrangements should be applicable for the active substance or intermediate only. Remove starting materials.<br><br><u>B.I.a.1.j:</u> Clarify that testing could be release and stability to allow clarity that in-process testing can be out of scope.<br>Extend to include drug device combinations.<br>According to EMQ Q&A on variation classification 7.2.13, the variation is needed only in case of a new site (not already authorised). This should be made clearer.<br>Wording for note provided. Addition or replacement of quality control testing arrangements should be applicable for the active substance or intermediate only. Remove starting materials. | Addition or replacement of a site where batch control/release and stability testing takes place applying physicochemical and/or microbiological analytical procedures for the active substance [Delete: or starting material] or intermediate or a drug component of combination product, if mentioned in the dossier.<br><br>Note: In case of transfer of QC testing activities applying physical, chemical and microbiological test methods to an already authorised site, there is no need to submit a variation. |
| 8 | 863<br>B.I.a.1.i<br>Documentation 2, 9 and 10 | EFPIA/VE | <u>Documentation 2:</u> Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology “declaration” could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or “confirmation” in the submission | <u>Documentation 2:</u><br>[Delete: A declaration] Confirmation from the marketing authorisation holder (or and the ASMF holder, where applicable), that the synthetic route, (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control |

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| | | | should be appropriate i.e., replace “declaration” by “confirmation.”<br><br>Documentation 9: Should be clarified what proof of GMP is needed for sites conducting biological etc. testing. The current documentation implies that proof of GMP is only required for sterilisation sites.<br><br>Documentation 10: Analytical transfers are governed by GMP requirements and this level of GMP documentation should not become part of standard submissions. Analytical transfer protocols are not a requirement of the CTD and should not need to be presented. Transfer reports can always be requested by the reviewer if there are concerns about a particular assay during review but it’s a retrograde step for this level of GMP documentation to become part of standard submissions. Also, at time of the new test site submission the protocol’s will most likely have been executed by the applicant so it doesn’t make sense to have the method transfer protocols submitted for review at this point. Therefore, remove Documentation 10. | procedures and specifications of the active substance and of the starting material/reagent/ intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.<br><br>Documentation 9:<br>Proof that the proposed site is appropriately authorised for the manufacturing operation concerned, i.e., for sterilisation of active substance.<br><br>[Delete: Documentation 10:<br>The analytical procedure transfer protocols in accordance with Eudralex Volume 4 Chapter 6 article 6.39 (which pre-define the acceptance criteria), from the old site to the new site (or new test laboratory). Depending on the variability of the specific method and the potential risk, to the quality, safety or efficacy of the product, posed by the proposed change, additional data such as a summary of the analytical procedure transfer test results may be required.] |
| 9 | 864<br>B.I.a.2 | EFPIA/VE | “A declaration from the marketing authorisation holder or and the ASMF Holder”<br>Document 4 two separate declarations should be provided (one from MAH and one from ASMF holder): considering that the change is relevant to the RP on which MAH has no visibility, only the declaration from ASMF holder could be sufficient | Stay with the old sentence: “A declaration from the ASMF Holder” |

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| 10 | 864<br>B.I.a.2.a condition 2 | EFPIA/VE | B.I.a.2.a) Minor change in the manufacturing process of the active substance<br>Condition 2.<br>For biological active substance/starting material/intermediate/reagent: the manufacturing steps remain the same and there are no changes to the manufacturing parameters (critical and non-critical PPs and IPCs) or to the specifications of the starting materials, intermediates, or active substance. There are no changes to the finished product.<br><br>Comments:<br>• The sentence 'There is no changes to the finished product.' needs to be removed, because it is stated again below for all products.<br>• A minor change to a process parameter for a biological AS is a very common change. For non-critical PPs and IPCs not meeting this condition should not result in a Type IB by default. The condition as written appears inconsistent with the definition of Critical PP in ICH Q8(R2).<br>• For biological reagents and starting materials science and risk-based approaches should be followed and therefore condition 2 should be amended. | For biological active substance/ [Delete: starting material/] intermediate [Delete:/reagent]: the manufacturing steps remain the same and there are no changes to the manufacturing parameters (critical PPs and IPCs), no changes to reagents which may impact the quality of the active substance/ intermediate, or to the specifications of the [Delete: starting materials,] intermediates, or active substance. |
| 11 | 864<br>B.I.a.2.a<br>Condition 2 | EFPIA/VE | B.I.a.2.a) Minor change in the manufacturing process of the active substance<br>Condition 2. | |

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| | | | For all: there are no changes to the finished product. Condition is too broad as this Type IA may be submitted grouped with accompanying variations to the product. | For all: “the change has no impact on Quality of the finished product" |
| 12 | 864<br>B.I.a.2.a<br>Conditions & Documentation | EFPIA/VE | Documentation 2 should clarify that batch data may be API or intermediate as appropriate (see similar wording currently used for B.I.a.3.a Documentation 2).<br><br>Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology “declaration” could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or “confirmation” in the submission should be appropriate. | See similar wording currently used for B.I.a.3.a Documentation 2.<br><br>Proposed change (preferred option):<br>“Confirmation from the marketing authorisation holder that [Delete: a full evaluation has been performed and]-the minor changes do not impact the quality, safety or efficacy of the active substance/medicinal product [Delete: (e.g. minor amendments to process description without actual process change, such as details of reagents (e.g. buffers, media preparation).] […]” |
| 13 | 864 B.I.a.2,<br>865 B.I.a.3<br>Documentation 3 | EFPIA/VE | In general, the requirement to provide copies of approved documentation, to support variations e.g. provision of approved specifications is redundant, in light of submissions being made in eCTD format. | B.I.a.2 Documentation 3:<br><br>[Delete: Copy of approved specifications of the active substance.]<br><br>B.I.a.3 Documentation 3:<br><br>[Delete: Copy of approved specifications of the active substance (and of the intermediate, if applicable).] |
| 14 | 865<br><br>B.I.a.3<br><br>c) d) | EFPIA/VE | There should either be no categorical exclusion of increases or decreases to the batch size for events for biologics (condition 3). The referenced categories c and d do not fully reflect the needed change categories for biologics. There should be a possibility to submit minor | Clarification for category c)<br><br>The change in batch size of a biological active substance/intermediate [Delete: requires assessment of the comparability] may have a |

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| | Condition 3<br><br>Documentation 5 | | changes to batch sizes for biologics as Type IB other than category d which is rather limiting. For instance, there could be minor changes in batch size, where a comparability assessment would be performed, but the change has a low risk for product quality impact. Comparability assessment could vary quite significantly in their extension. The default for biologics should not be Type II. Applicants should be able to utilise risk-based approaches as per ICH. An amendment to change category d) is required to address these low-risk changes to reduce regulatory burden for the health authorities and industry. This would facilitate the introduction of higher capacities in a timely manner to avoid supply risks. Further category c should be clarified in terms of comparability assessment. In this context, documentation 5 should be adapted to account for situation when for Type IB comparability assessments are performed. Category d should still be possible even if comparability is performed, it should rather be related to significance of impact than need for comparability studies.<br><br>In addition, for change category d) there is confusion about the change in scale through a duplication of line as there are different situations.<br><br>For a batch size increase through duplication of line with no process changes or small process changes, no impact on the quality of the active substance is expected, and therefore it should | significant impact on the quality, safety or efficacy of the medicinal product<br><br><u>Amend the current category d):</u><br><br>The scale for a biological active substance / intermediate is increased / decreased without process change [Delete: (e.g. duplication of line)] or without significant impact on the quality, safety or efficacy of the medicinal product<br><br><u>Documentation 4:</u><br><br>[Delete: A declaration] Confirmation from the marketing authorisation holder (and the ASMF holder as appropriate) that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.<br><br><u>Documentation 5:</u><br><br>For biological active substance, a justification that an assessment of comparability is not required (if applicable) or that changes do not have a significant impact on the quality, safety or efficacy of the medicinal product. |

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| | | | be classified as Type IB (instead of Type II if small process changes are involved). A low-risk change should be proportionate to the level of change.<br><br>In case of a duplication of line without a batch size increase and no other changes, this is currently handled according to EMA's Questions and Answers on classification of changes No. 2.9. *"What changes in manufacturing sites, buildings and rooms are covered by the company Quality Assurance System (GMP)? Rev. May 2018"* which states that a new filing line identical to an already approved one in an authorised room, building, manufacturing site does not require a variation, there is ambiguity over what does and does not require a variation. Suggest that "(e.g. duplication of line)" is removed to avoid inconsistencies (while maintaining the overall scope of the variation category). Ambiguity should be avoided when stating duplication of line in the variation guideline. It should be considered to add a note on this topic.<br><br>In order to avoid ambiguity, it is proposed to remove the "e.g. duplication of line" from the category.<br><br>As regards the documentation 4 for category d): Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and | |

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| | | | proliferation. A statement or “confirmation” in the submission should be appropriate. In addition, for consistency with condition 1, confirmation should only be required to state that specifications for starting materials and reagents are the same as those already approved. | |
| 15 | 866<br>B.I.a.4 f)<br>Condition 6 | EFPIA/VE | Regarding condition 6 for change B.I.a.4.f, IPC methods for biologics are not inherently more complicated than those used for small molecules. Minor changes to IPC tests for biologics should be able to be reported as a Type 1A. Therefore, the condition should be removed. | [Delete: Condition 6:<br>The new analytical procedure is not a biological/immunological/immunochemical procedure] |
| 16 | 866<br>B.I.a.4 b) g)<br>Documentation 4 | EFPIA/VE | A replacement of a non-critical or equivalent test procedure should be possible under a Type IA. Thus, reporting category should be risk-based and connected with a condition for Type IA that the procedure is even better. If this condition is not fulfilled, change would be classified as Type IB by default. In addition, it should be clarified that this change category also refers to the corresponding test procedure.<br>Batch analysis data should not be required for a change to an IPC test under category B.I.a.4 b) and g). To support the adequacy of an added or replaced IPC test, data should be provided showing the new method is capable of monitoring the attributes to the same or better extent as the current method. Thus documentation (data/justification) for this | g) Replacement of an in-process test and/or analytical procedure<br>Type [Delete: IB] IA<br>Additional condition to be fulfilled:<br>7) The new in-process test and/or analytical procedure exceeds previous method capabilities and provides an increased control or does not refer to a critical IPC.<br>Documentation 4:<br>Documentation that new test is an adequate in-process control including (as appropriate) batch analysis data on two production batches [Delete: [3 production batches (unless otherwise justified) for biologicals]] of the active |

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| | | | should be provided rather than batch analysis data. Of course, if deemed necessary it could be complemented by batch analysis data but it should not be standard requirement. In addition, there should not be a different requirement for biologics per se but also risk-based. | substance/intermediate [Delete: for all specification parameters.] |
| 17 | 866<br>B.I.a.4. c)<br>Condition 7 | EFPIA/VE | The note infers that all changes to non-critical process parameters need to be reported as Type IB and II, which should not be the case. Rewording for the text proposed.<br>For condition 7 there is unclarity about the listed critical attribute “assay”. In any case, as this listing leads to unclarity and too many restrictions as to what is critical or not which should be based on the company’s risk assessment and thus proposed to be deleted. | Note:<br>This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled [Delete: as Type IB or II variations as appropriate] using science and risk-based approaches when defining the reporting category.<br>Condition 7:<br>The in-process test does not concern a critical attribute [Delete: , for example:<br>• assay<br>assay,<br>• purity,<br>• impurities (except when a solvent is no longer used in the manufacture of the active substance),<br>• a critical physical characteristic (for example: particle size, bulk or tapped density),<br>• identity test,<br>• or water content.] |

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| 18 | 866<br>B.I.a.4<br>d) h) | EFPIA/VE | For change d) the comma after “limits” in the text (“…test limits, which…”) indicates a statement of qualifying fact that in any circumstance any widening of an approved IPC may be regarded as having significant impact on quality. This appears to raise the bar for widening of IPC based on historical data and where IPC were initially established based on fewer data and set conservatively. In that case, changes could be reasonably foreseen as a type 1B on a risk-based approach. It is proposed to delete the respective comma and as there is no category for widening of limits which do not have a significant impact on the overall quality of the active substance, it is proposed to add a new change category to address this gap. Proposed to add between current d) and current e). | d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance<br>h) Widening of the approved in-process test limits which does not have a significant effect on the overall quality of the active substance<br>Procedure Type:<br>IB<br>Conditions to be fulfilled:<br>1, 2, 4<br>Documentation:<br>1, 2, 4, 6 |
| 19 | 866<br>B.I.a.4<br>b) and f) | EFPIA/VE | With regard to provision b) and f), while it is recognized that analytical procedures for IPCs might be in some dossiers, they are not required as per EU guideline on chemistry of active substances. Therefore, it is proposed to add the proposed text: "if applicable" | b) Addition of new in-process test and limits with its corresponding analytical procedure, if applicable.<br>f) Minor change of an analytical procedure for an in-process test, if applicable. |
| 20 | 867/868<br>B.I.a.5/6 | EFPIA/VE | It is recommended to combine B.I.a.5 and 6 as flexibility is required also for seasonal updates particularly considering rest of the world dynamics. In the combined section, category a and b currently under B.I.a.6 should be | <u>B.I.a.5:</u><br>Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza, human coronavirus or other vaccine that has the potential to address a public health emergency in the Union.<br>a) Replacement or, upon agreement of the relevant authorities, addition of a serotype, strain, |

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| | | | maintained (which allows co-existence if pre-agreement is granted).<br><br>Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or "confirmation" in the submission should be appropriate.<br><br>Documentation 1: Should be confirmation instead of declaration. "Declaration that the remaining product presentation(s) are adequate for the dosing instructions and duration as mentioned in the summary of product characteristics, and the deletion has been agreed in principle with the Agency."<br><br>Documentation: 3. Should be confirmation instead of declaration. "Declaration that the deletion of the serotype, strain, antigen or coding sequence is no longer appropriate in relation to the epidemiological evolution of the human virus of concern" | antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human influenza vaccine, human coronavirus vaccine or other vaccine that has the potential to address a public health emergency in the Union<br>b) Deletion of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human influenza vaccine, human coronavirus vaccine or other vaccine that has the potential to address a public health emergency in the Union<br>Documentation 1: ~~Declaration~~ Confirmation that the remaining product presentation(s) are adequate for the dosing instructions and duration as mentioned in the summary of product characteristics, and the deletion has been agreed in principle with the Agency."<br>Documentation: 3. [Delete: Declaration] Confirmation that the deletion of the serotype, strain, antigen or coding sequence is no longer appropriate in relation to the epidemiological evolution of the human virus of concern" |
| 21 | 864<br>B.I.a.2 | EFPIA/VE | The classification proposed is no more in line with the Q&A classification of the change from EMA for the new working cell bank. The proposal is to add the specific changes related | Addition or replacement of a site responsible for storage or generation of the Master Cell Bank and/or Working Cell Banks when already described in the dossier (type IA) |

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| | | | to WCB/WSL in B.I.a.2 as done in B.I.b.3 for change to reference standard. | |

***B.I.b) Control of active substance***

| | Please insert reference to relevant scope or section *(e.g. B.I.a.1.a, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | General & 871<br>B.I.b.2.h) | EFPIA/VE | It appears that there are several instances where biologic products that may have the same types of manufacturing, control and/or product changes are excluded from being categorized in the same variation category.<br>It is recommended to re-visit this exclusion. There is currently a long history of industry experience with well characterized biologics, such as monoclonal anti-bodies and vaccines. While it is acknowledged, there continue to be new advancements in this space, it is recommended to separate well characterized biologics from more recent, novel technologies to enable a risk and scientific approach to managing change.<br>Please consider the example below:<br>There is an inconsistency in the conditions for d) "Other change to an analytical procedure | Recommend to revisit change categories relating to well characterised biologics, whilst specifically updating the below example as follows:<br>B.I.b.2.h) Delete Condition 4 under “Conditions to be fulfilled” column.<br>In addition, delete Condition 4 completely from the conditions section of B.I.b.2 since it is not applicable to any change. |

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| | | | (including replacement or addition) for the active substance" and h) "Other change to an analytical procedure (including replacement or addition) for a starting material/reagent/intermediate". Condition 4 excluding biological/ immunological/ immunochemical procedures is applied to starting material/ reagent/ intermediate but not to active substances. The condition should be removed for all minor changes to these assays and not applied in any situation as long as confirmation can be provided that the change is only minor and has no significant impact on the assay performance. | |
| 2 | 870<br>B.I.b.1 | EFPIA/VE | The current presentation of B.I.b.1 makes it difficult to differentiate between different materials (active substance/intermediate/starting material/reagent) included within the scope of the change. Consequently, the proposed change categories are not fully reflective of the risk-based approach adopted elsewhere in the guideline such as B.I.b.2. Including active substance, intermediates, starting materials, reagents within the same change classification is disproportionate. For example, it is unnecessarily restrictive for reagents and starting materials that should be controlled mostly under the auspices of GMP (EU GMP Part II (7.3) and not via licensing. The section would therefore greatly benefit by separating the | Propose two options for consideration:<br><u>Option 1:</u><br>Create the following 4 sections under the main B.I.b.1 variation category header:<br>• **Change to specification of active substance/ starting material/ intermediate** – include original change categories e), b), c), d), l);<br>• **Change to specification of active substance/ intermediate** – include original change categories g), a), f), h), i), j), k);<br>• **Change to specification of starting material** – this would create new change categories m), n);<br>• **Change to specification of critical reagent** – this would create new change categories o), p), q). |

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| | | | changes per material type based on the risk associated with the change. | <u>Option 2:</u><br><br>Create 4 separate change codes relating to Change in Specification under the B.I.b) Control of Active Substance section:<br><br>• B.1.b.1 (Active substance);<br>• B.I.b.x (Intermediate);<br>• B.I.b.x (Starting Material);<br>• B.I.B.x (Reagent). |
| 3 | 870<br><br>B.I.b.1 | EFPIA/VE | With reference to Comment 2 above the overall presentation of changes under one overarching variation category header results in the classification of a number of change categories that do not appear commensurate with the potential risks. The variation category covers materials that do not have the same risk factors when considering effect on overall quality of the active substance and/or the finished product, and it would be beneficial for them to be considered independently.<br><br>For example, the relative risk to the quality of the active substance/finished product arising from a change outside the approved specification for an intermediate versus a reagent is different, yet the classification as written proposes a type II variation in both scenarios. Similarly, it should be possible to justify the difference between a change outside of the approved active substance specification with the potential to impact the quality of the active substance and/or the finished product | In line with Option 1 in Comment 2 above propose to update B.I.b.1 change categories as follows:<br><br>CHANGE TO SPECIFICATION OF ACTIVE SUBSTANCE/STARTING MATERIAL/INTERMEDIATE<br><br>a) Deletion of a specification attribute which may have a significant effect on the overall quality of the active substance and/or the finished product.<br><br>Procedure Type II<br><br>b) Change within the approved specification acceptance criteria.<br><br>Procedure Type IA<br><br>c) Addition of a new specification attribute and its corresponding analytical procedure, if applicable.<br><br>Procedure Type IA |

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| | | | (Type II) versus a change outside of the approved active substance specification with no impact to quality of the active substance and/or finished product (Type IB).<br><br>An additional example relates to a Type IB classification to alter specification for non-critical reagents which is not aligned to the minimal risk proposed to the medicinal product. Similarly skip testing of reagents and starting materials is controlled under EU GMP Part II (7.3) hence an additional wording to clarify the scope of the original change category B.I.b.1.k is proposed. | d) Deletion of a non-significant or an obsolete specification attribute (*).<br><br>Procedure Type IA<br><br>e) Replacement of a specification attribute and its corresponding analytical procedure<br><br>Procedure Type IB<br><br>CHANGE TO SPECIFICATION OF ACTIVE SUBSTANCE / INTERMEDIATE<br><br>f) Change outside of the approved specification acceptance criteria for active substance/ intermediate which may have a significant effect on the overall quality of the active substance and/or the finished product.<br><br>Procedure Type II<br><br>g) Change within the approved specification acceptance criteria for medicinal products subject to Official Control Authority Batch Release<br><br>Procedure Type IAIN<br><br>h) Change outside of the approved specification acceptance criteria for the active substance with no significant effect on the overall quality of the active substance and/or the finished product |

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| | | | | Procedure Type IB<br><br>Document Supplied 2, 5, 6<br><br>i) Change outside of the approved specification acceptance criteria for intermediate with no significant effect on the overall quality of the active substance and/or finished product<br><br>Procedure Type IA<br><br>Document Supplied 1, 2, 7<br><br>Condition 8 – There is no significant effect on the overall quality of the active substance and/or the finished product as a result of this change<br><br>j) Change in specification attribute for the active substance from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State<br><br>Procedure Type IB<br><br>k) Change of the analytical marker or widening of the acceptance criteria of the analytical marker (other extracts) for a herbal active substance.<br><br>Procedure Type IB |

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| | | | | l) Change in the testing of specification attribute, from routine to non-routine testing (skip or periodic testing) for an active substance or intermediate<br><br>Procedure Type IB<br><br>CHANGE TO SPECIFICATION OF STARTING MATERIAL<br><br>m) Change outside of the approved specification acceptance criteria for starting material with no significant effect on the overall quality of the active substance and/or the finished product.<br><br>Procedure Type IA<br><br>Document Supplied 1, 2, 7<br><br>Condition 8 – There is no significant effect on the overall quality of the active substance and/or the finished product as a result of this change<br><br>n) Change outside of the approved specification acceptance criteria for starting material which may have a significant effect on the overall quality of the active substance and/or the finished product.<br><br>Procedure Type IB<br><br>Document Supplied 1, 2, 7 |

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| | | | | CHANGE TO SPECIFICATION OF CRITICAL REAGENT<br><br>o) Change outside of the approved specification acceptance criteria for the critical reagent where mentioned in the dossier<br><br>Procedure Type IA<br><br>Document Supplied 1, 2, 7<br><br>Condition 8 – There is no significant effect on the overall quality of the active substance and/or the finished product as a result of this change<br><br>p) Deletion of a non-significant or an obsolete specification attribute (*)<br><br>Procedure Type IA<br><br>Document Supplied 1, 2, 7<br><br>Condition 1, 8 – (Condition 8: There is no significant effect on the overall quality of the active substance and/or the finished product as a result of this change).<br><br>q) Replacement of a specification attribute with its corresponding analytical procedure<br><br>Procedure Type IA |

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| | | | | Document Supplied 1, 2<br><br>Condition 8 – There is no significant effect on the overall quality of the active substance and/or the finished product as a result of this change<br><br>In line with Option 2 in Comment 2 above propose to update B.I.b) Control of Active Substance as follows:<br><br>Split into 4 distinct change codes relating to Change in Specification under the B.I.b) Control of Active Substance section. An example of one such change code of active substance is provided below as B.I.b.1.<br><br>B.I.B.1 CHANGE TO SPECIFICATION OF ACTIVE SUBSTANCE<br><br>a) Change within the approved specification acceptance criteria for medicinal products subject to Official Control Authority Batch Release<br><br>Procedure Type IAIN<br><br>b) Change within the approved specification acceptance criteria. |

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| | | | | Procedure Type IA<br><br>c) Addition of a new specification attribute with its corresponding analytical procedure, if applicable.<br>Procedure Type IA<br><br>d) Deletion of a non-significant or an obsolete specification attribute (*).<br>Procedure Type IA<br><br>e) Deletion of a specification attribute which may have a significant effect on the overall quality of the active substance and/or the finished product.<br>Procedure Type II<br><br>f) Change outside of the approved specification acceptance criteria for the active substance with no significant effect on the overall quality of the active substance and/or the finished product<br>Procedure Type IB<br>Document Supplied 2, 5, 6<br><br>g) Change outside of the approved specification acceptance criteria for active substance which may |

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| | | | | have a significant effect on the overall quality of the active substance and/or the finished product.<br><br>Procedure Type II<br><br>i) Change in specification attribute for the active substance from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State<br><br>Procedure Type IB<br><br>j) Change of the analytical marker or widening of the acceptance criteria of the analytical marker (other extracts) for a herbal active substance.<br><br>Procedure Type IB<br><br>k) Change in the testing of specification attribute, from routine to non-routine testing (skip or periodic testing) for an active substance<br><br>Procedure Type IB<br><br>l) Replacement of a specification attribute-and its corresponding analytical procedure<br><br>Procedure Type IB |

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| 4 | 870<br>B.I.b.1 | EFPIA/VE | The term reagent would benefit from further clarification. It is understood that reagent does not refer to analytical reagents or reference standards but materials used within the manufacturing process of the active substance such as solvents. It is unclear if the term is also intended to include raw materials such as culture media used in biological processes as defined in 2009/120/EC. Inclusion of all reagents within the scope of this change code is excessive and will lead to undue regulatory burden for both Industry and the Agencies. The scope for reagents should be limited to those reagents used during the manufacturing process considered critical as mentioned in the dossier. | Propose to update text to clarify applicability to Critical reagents only.<br><br>Please consider clearly defining the term reagent as it applies to the B.I.b) change codes. |
| 5 | 870<br>B.I.b.1 | EFPIA/VE | Finally, a risk-based approach to the necessity to provide supportive data is encouraged. Commercial batch data is of little relevance in minor / moderate changes to specifications of active substance / intermediate / starting materials. There is no value in commercial batch data of active substance for which specifications have been altered as it is expected that the batch will conform to the revised specification. This requirement is grounded in the basis of specification limits reflecting historical commercial experience and the concept of “tightening” rather than allowing for a more clinical (safety and efficacy) based approach. For the most part the respective analytical method validation status is more appropriate. This might | Propose to update text as follows:<br><br>Delete Documentation 4.<br><br>Update Documentation 7 as follows:<br><br>Justification from the MAH or ASMF Holder as appropriate that with the change, the control strategy remains suitable for the purpose of controlling product quality |

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| | | | not be the case for changes that may have significant impact but proposals for reduced commercial batch data in that circumstance could even be proposed. A risk based approach for minor change should be facilitated utilising historical / development / characterisation / method validation data in the context of justifying the continued applicability / relevance of the control strategy. As such propose to delete Document 4 from all minor variation categories. In parallel propose to update Document 7 to focus on the control strategy. | |
| 6 | 870<br>B.I.b.1.k | EFPIA/VE | Although B.I.b.1.k) refers to non-routine testing (skip or periodic testing) it is recommended to have a distinct variation category for real-time release testing for active substance and intermediates, as per finished product (B.II.d.3). | Propose to add a variation category to align with finished product:<br>Add variation category after B.I.b.2<br>Variations related to real-time release testing in the manufacture of the intermediates and active substance |
| 7 | 871<br>B.I.b.2.b | EFPIA/VE | Typographical error.<br>Substance appears twice. Propose to delete. | Propose to update B.I.b.2.b) as follows:<br>Deletion of an analytical procedure for the active substance if an alternative procedure is already authorized. |
| 8 | 871<br>B.I.b.2.c | EFPIA/VE | B.I.b.2.c) has been classified as a Type II. However, it is not clear why there is a higher burden for this type of method when applied to an active substance compared to a starting | Propose to update B.I.b.2.c) classification as follows:<br>Procedure type: Type IB |

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| | | | material/intermediate as detailed in B.I.b.2.g) which has been classified as Type IB. | |
| 9 | 871<br>B.I.b.2.c) & g) | EFPIA/VE | It is not clear why a type II variation would be required if a Ph. Eur. method was introduced. This category should only be for non-compendial methods hence a new change category is proposed relating to Ph. Eur. | Propose to update B.I.b.2 as follows:<br>Introduction of the same change category, but under both sub-headings (Change to the analytical procedure for the active substance & Change to analytical procedure for starting materials/reagent/intermediate used in the manufacturing process of the active substance):<br>Introduction or replacement with a biological/immunological/immunochemical analytical procedure to comply with of the European Pharmacopoeia or the national pharmacopoeia of a member state.<br>Procedure Type: IA<br>Condition: 1<br>Documents to be supplied: 1, 2 |
| 10 | 871<br>B.I.b.2.d | EFPIA/VE | B.I.b.2.d) has been classified as a Type IB but has both documents and conditions associated. Since Type IB variations don't have conditions this change should be classified as a Type IA. | Propose to update B.I.b.2.d) classification as follows:<br>Procedure Type: IA |
| 11 | 871<br>B.I.b.2.d | EFPIA/VE | As with B.I.b.2.h) Condition 6 should not be associated with B.I.b.2.d) as this is not applicable for this change. | Propose to update text as follows: |

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| | | | | B.I.b.2.d) - delete condition 6. |
| 12 | 871<br>B.I.b.2.e<br>Document 2 | EFPIA/VE | Considering that validation data is not always required for analytical procedures for intermediates, reagents and starting materials (e.g. see Guideline on the chemistry of active substances), biological tests are covered under a Type IB scope, and condition 1 requires that appropriate validation studies have been conducted, the requirements for comparative studies should be refined and hence Document 2 should be updated. | Propose to update Document 2 as follows:<br>Comparative validation results, or if justified comparative analysis results showing that the current analytical procedure and the proposed one are equivalent. This requirement is not applicable:<br>- In case of an addition of a new analytical procedure unless the new analytical procedure is added as an alternative procedure to a current one.<br>- In case of starting materials/reagents/intermediates, for non-critical specification attributes. |
| 13 | 871<br>B.I.b.2 e) | EFPIA/VE | Typographical error:<br>Two forward slash. Propose to delete extra forward slash. | Propose to update B.I.b.2.e) as follows:<br>Minor change to an analytical procedure for starting material/reagent/ intermediate. |
| 14 | 871<br>B.I.b.2.e) & h) | EFPIA/VE | The difference between change categories e) and h) is very minimal in terms of "minor change" and "other change".<br>It is proposed to combine e) and h). Since both are a Type IA this shouldn't be a concern and propose biological procedures should be treated in the same way.<br>Condition 3 as written refers to a situation where a method is replacing an existing one and does not consider the introduction of a method. | Propose to update section B.I.b.2 as follows:<br>Combine changes e) and h) to create the following change:<br>Replacement or addition of, or any minor change to, analytical procedure for starting material/reagent/intermediate<br>Conditions: 1,2,3,5 |

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| | | | Hence it is proposed to add a caveat to the existing text, “if applicable”. | Document to be supplied: 1, 2<br><br>Amend condition 3 as follows:<br><br>The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method), if applicable. |
| 15 | 871<br><br>B.I.b.2<br><br>Conditions | EFPIA/VE | Typographical error:<br><br>There is an empty row between conditions 5 and 6. Propose to delete. | Propose to update conditions as follows:<br><br>Deletion of the empty row. |
| 16 | 871<br><br>B.I.b.2 | EFPIA/VE | B.I.b.2 refers to reagents in many places. The term reagent would benefit from further clarification. It is understood that reagent does not refer to analytical reagents or reference standards but materials used within the manufacturing process of the active substance such as solvents. It is unclear if the term is also intended to include raw materials such as culture media used in biological processes as defined in 2009/120/EC.<br><br>Additionally, inclusion of all reagents within the scope of this change code is excessive and will lead to undue regulatory burden for both Industry and the Agencies. The scope for reagents should be limited to those reagents used during the manufacturing process considered critical as mentioned in the dossier. | Propose to update text to clarify applicability to Critical reagents only.<br><br>Please consider clearly defining the term reagent as it applies to the B.I.b) change codes. |

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| 17 | 872;<br>B.I.b.3.f) | EFPIA/VE | The risk of extending shelf life of a reference standard being managed under protocol is not commensurate with the risk of implementing a new reference standard nor is the current proposal for B.I.d.1.a) 5.<br><br>Change a and note 1 are clear where there is no approved qualification protocol then a variation submission analogous to respective change in DS is required - this would default an affected reference standard as having life extended by real time stability data not in accordance with an approved stability protocol or an extension an approved stability protocol or an extension based on extrapolation of stability data in accordance with relevant stability guidelines (B.I.d.1.a.4). If it is subject to a qualification protocol note 2 is pertinent. An approved stability protocol relating to a reference standard is a basic qualification protocol for the purpose of managing reference standard shelf life. Under the circumstances note 2 prevails. Category f should be removed. | Propose to update text as follows:<br><br>Change B.I.b.3.f) should be deleted. |
| 18 | 872<br>B.I.b.3<br>Document 3 | EFPIA/VE | The guideline should be clarified by referring to the 3.2.S.5 reference standard protocol to avoid confusion with the active substance stability protocol in Section 3.2.S.7.2. | Propose to update Condition 3 as follows:<br><br>Confirmation that stability studies have been done to the currently approved protocol in Section 3.2.S.5 Reference Standards or Materials. The studies must show that the agreed relevant specifications are still met. |
| 19 | 872 | EFPIA/VE | We welcome the introduction of this new category that reflects the Q&A document EMEA-H-19984/03 Rev. 108 “European Medicines | Proposal is as follows: |

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| | B.I.b.3 | | Agency post-authorisation procedural advice for users of the centralised procedure". It is also recommended to add a dedicated change category for the introduction and qualification of new working cell bank (and new working seeds) in line with question 7.2.7 of the aforementioned Q&A document. For clarity considerations for changes relating to introduction of new MCB should also be included. | Recommend to construct entirely new change category relating to working cell back (and new working seeds) accounting for changes described in Q&A document, and possibly for MCB. |
| 20 | 872<br>B.I.b.3 | EFPIA/VE | New category proposed for a minor modification to an approved qualification protocol<br><br>Potentially add a third note that qualifies other and minor changes as being default equivalent to equivalent change categories in B.I.b.1 and B.I.b.2 respectively. New category proposed for a minor modification to an approved qualification protocol. | Propose to update B.I.b.3 as follows:<br><br>Additional Change category with additional note parenthesis:<br><br>B.I.b.3.g) Minor change to the qualification protocol for the replacement of an in-house reference standard or preparation (3)<br>Procedure Type: 1A<br>Conditions: 1 - Change does not concern acceptance criteria of the protocol<br>Documents to be supplied: 1<br>Note 3 - Other and minor changes to the qualification protocol are anticipated to be analogous to the equivalent Type 1B or Type 1A changes described in B.1.b.1 and B.1.b.2 |

***B.I.c) Container closure system***

| | Please insert reference to relevant scope or section *(e.g. B.I.a.1.a, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 874<br>B.I.c.1.a/c | EFPIA/VE | The conditions for biological medicinal products are not appropriately risk-based given that there are no limits provided for the type of change to the immediate container.<br>The default for biological products would more appropriately be Type IB rather than Type II when stored frozen.<br>The risk of impact from leachates, changes in product contact area or headspace would be minimal. There would be thorough analytical comparability with comparative stability at accelerated conditions as well as post-approval real-time stability to support the low risk and mitigate the unforeseen. | Delete biological active substance from Condition 3.<br>"The active substance is not a sterile active substance, or liquid active substance [Delete]." |
| 2 | 874 | EFPIA/VE | Condition 2 and documentation 5: Concepts from revision of ICH Q1 intending to clarify applicability of requirements across development and lifecycle (risk-based approaches based on change) and ICH Q12 principles may be used to determine the need and extent of studies required to support changes. Therefore, alternative wording could be proposed. | (…) at least two pilot or industrial scale batches, covering a minimum period of 3 months (…) Alternative scientifically justified approaches aligning with European and international scientific guidelines may be acceptable. |

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| 3 | 874<br>B.I.C.1.b) | EFPIA/VE | Flexibility should be added e.g. Type IB when there are like for like changes. The default for all should not be Type II. | Create an additional type IB change code |
| 4 | 874<br>B.I.c.1.d) Condition 4 | EFPIA/VE | Recommend removing condition 4 as any packaging remaining in the dossier will already have been assessed and deemed fit for purpose | Condition 4. [Delete] |
| 5 | 874<br>B.I.c.1<br>Conditions | EFPIA/VE | In condition 3 liquid AS is redundant. | Conditions<br>3. The active substance is not a sterile active substance [Delete] or biological active substance. |
| 6 | 874<br>B.I.c.1, Documentation | EFPIA/VE | In documentation 3, it is unrealistically absolute to state "…. proof must be provided that no interaction between the content and the packaging material ….” and “no migration of components”, or “no loss of components”<br>There will always be interaction between the product and the immediate container. Examples of types of supporting data are provided, but the important point is that any migration or loss is evaluated, risk assessed against the impact of the change on product quality. | Where appropriate, proof must be provided that [delete] the interaction between the content and the packaging material has no impact on the active substance quality [delete] (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack that impacts quality of the active substance), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation of the Union on plastic material and objects in contact with foodstuffs. |
| 7 | 874<br>B.I.c.1, Documentation | EFPIA/VE | Documentation 4 does not account for the new Quality or Platform Technology Master File (PTMF). | A declaration from the marketing authorisation holder or the ASMF/QMF/PTMF holder as appropriate that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the |

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| | | | | disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). |
| 8 | 875<br>B.I.c.2 | EFPIA/VE | Change in the specification attribute and/or acceptance criteria of the immediate packaging of the active substance<br><br>Comment: Change outside of the approved acceptance criteria is missing, both with or without impact on product quality. | Add the case:<br><br>Change outside of the approved acceptance criteria which may have a significant effect on the overall quality of the active substance and/or the finished product<br><br>Proposed category Type II<br><br>Add the case:<br><br>Change outside of the approved acceptance criteria which does not have a significant effect on the overall quality of the active substance and/or the finished product<br><br>Proposed category Type IB |
| 9 | 875<br>B.I.c.2 condition 2. | EFPIA/VE | Typo: “safety” | “safety” |
| 10 | 875<br>B.I.c.2 Documentation 5. | EFPIA/VE | Verb agreement and wordiness | “Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as |

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| | | | | appropriate, that the specification attribute is non-significant [Delete]or [Delete] obsolete." |
| 11 | 875<br>B.I.c.2, Documentation | EFPIA/VE | Documentation 4 and 5 do not account for the new Quality or Platform Technology Master File (PTMF). | 4. Justification/risk assessment from the marketing authorisation holder or the ASMF/QMF/PTMF Holder, as appropriate, that the specification attribute are non-significant, or that the specification attribute is obsolete.<br><br>5. Justification from the marketing authorisation holder or the ASMF/QMF/PTMF Holder, as appropriate, of the new specification attribute and the acceptance criteria. |
| 12 | 875<br>B.I.c.2 (as an example) | EFPIA/VE | Suggest to use "critical" in stead of "significant", as critical is more in line with wording used in ICH guidelines.<br><br>This comment applies in several variation types/conditions | Deletion of a non-critical or obsolete specification attribute (*) parameter (e.g. deletion of an obsolete parameter). |
| 13 | 875<br>B.I.c.2.a) | EFPIA/VE | In all other instances, "Tightening of specifications" was replaced with "Change within the specification acceptance criteria" - e.g. B.I.b.1.a and b, B.II.e.4.a and B.II.d.1.a. The wording should be aligned for B.I.c.2.a as well | Change within the approved specification acceptance criteria. |
| 14 | 876<br>B.I.c.3 | EFPIA/VE | Typo – there is no condition 5 in revised guidance. | Replace condition 5 with condition 4. |

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| 15 | 877<br>B.I.c.4 | EFPIA/VE | Change of a secondary packaging component of the active substance (including replacement or addition), when mentioned in the dossier.<br><br>Secondary packaging components, where described, that do not play a functional role, will not impact Quality of the API and therefore should not be subject to variation.<br><br>This information can be regarded as supportive and managed in Company's PQS (Pharmaceutical Quality System) based on a risk assessment. The relevant sections can be updated at next occasion to avoid unnecessary challenges to supply continuity in EU and reliant markets. | B.I.c.4 Change of a secondary packaging component of the active<br>substance (including replacement or addition), [Delete] that plays a functional role<br><br>Condition 1:<br>The secondary packaging [Delete] is not less protective than the approved one. |

***B.I.d) Stability***

| | Please insert reference to relevant scope or section *(e.g. B.I.a.1.a, Conditions, Documentation)* | Stakeholder name<br>*(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 879<br>B.I.d.1.a) 3 | EFPIA/VE | Ambiguous text; does the "not" apply to both or just the first one?<br><br>It is assumed the intent is to have a distinction between extrapolation (small molecules per | Propose to add a comma:<br><br>"Extension of the retest period/storage period of the active substance based on extrapolation not in accordance with relevant stability guidelines, or based on stability modelling" |

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| | | | current ICH Q1E decision tree) and stability modelling.<br><br>If this assumption is correct then the guideline needs to explain.<br><br>The proposed edit assumes Type II variation for extrapolation not in accordance to guidelines and Type II variation for stability modelling<br><br>A comma is needed to clearly separate 'stability modelling' from 'extrapolation not in accordance with guidelines'. This is the assumed intent. | An explanation of 'extrapolation' versus 'stability modelling' is critical. |
| 2 | 879<br><br>B.I.d.1<br><br>Conditions /<br><br>Documentation | EFPIA/VE | The requirement to provide copies of approved documentation, to support variations e.g. provision of approved specifications, is redundant when submissions are in eCTD format.<br><br>Therefore, it is proposed to delete this requirement.<br><br>It could be considered to add a condition that the specification should be unchanged.<br><br>This approach should be added to all change categories that require a copy of the approved specification:<br><br>B.I.a.2: Documentation 3<br><br>B.I.a.3: Documentation 4 | Conditions:<br><br>5. The specifications of the active substance remain the same.<br><br>Documentation:<br><br>3. [Delete text] |

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| | | | B.I.e.5: Documentation 5<br>B.II.b: Documentation 4<br>B.II.b.3: Documentation 6<br>B.II.b.4: Documentation 3<br>B.II.c.4: Documentation 4<br>B.II.f: Documentation 3<br>B.II.g.5: Documentation 5 | |
| 3 | 879<br>B.I.d.1 Conditions | EFPIA/VE | Condition 3 is impractically stringent on trends, especially for biologics.<br>Edit made to align with B.I.d.1.a.4 where real-time data are 'supportive'. | Stability studies have been performed in accordance with a currently approved stability protocol. Supportive real time data are submitted. All batches meet their pre-defined specification at all time points. No change in trends have been observed. |
| 4 | 879<br>B.I.d.1 Documentation | EFPIA/VE | It is unnecessary to state or increase the expectation to "3 batches (unless otherwise justified)" for biologicals and should be deleted.<br>ICH Q1 current and revision (Tier 1 guideline) would state the number of batches for post-approval changes on an appropriate science & risk basis. Stating "at least two" is sufficient.<br>Increasing the burden for biologicals risks contradiction with ICH guidance. | 1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format. This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on, unless otherwise justified, at least two [delete text] pilot or production scale batches of the active substance in the authorised packaging material and covering the duration of the requested re-test period/ storage period or requested storage conditions. |
| 5 | 879<br>B.I.d.1 | EFPIA/VE | Remove requirement for Documentation 2 for reduction of re-test period/storage period (B.I.d.1.a.1). | 1, [delete text], 3 |

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| | Documentation | | Confirmation that stability studies have been done to the currently approved protocol would have been provided previously and adds no value to reducing the re-test period/storage period. | |
| 6 | 879 | EFPIA/VE | Empty column in ”b) storage conditions” | Deletion of the empty column |

***B.I.e) Additional regulatory tools***

| | Please insert reference to relevant scope or section *(e.g. B.I.a.1.a, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 886 & 887<br>B.I.e.6 & B.I.e.7 | EFPIA/VE | Whilst it is welcome to see mention made of the Product Lifecycle Management Document and the implication of the adoption of the broader concepts in ICH Q12, it is unclear how this will be implemented.<br>It is proposed to extend the scope to encompass all quality changes as it is described in the classification guideline.<br>Furthermore, clarification is sought on the path forward for this and any associated timescale. The additions are welcomed and should be complemented with a Q&A/Note for Guidance from the Agency with further clarity on application with examples. | N/A |

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| 2 | 881<br>B.I.e.1 b) | EFPIA/VE | B.I.e.1 b) introduces MODR which is appreciated. However, the reporting type appears to be disproportionate compared to the risk level as MODR would only enable some changes for a given analytical technology. | It would be recommended to have a specific category for introduction or extension of a MODR as a type IB to encourage enhanced analytical development. |
| 3 | 882<br>B.I.e.2 | EFPIA/VE | Introduction of a post approval change management protocol related to the active substance as the acronym is used afterwards. | "Introduction of a post approval change management protocol (PACMP) related to the active substance." |
| 4 | 884<br>B.I.e.4 Changes to an approved change management protocol | EFPIA/VE | More flexibility is required on provision for documentation item 1 as some changes can be easily justified, even if they are broader than the currently approved protocol | 1. Declaration that the changes do not change the overall strategy defined in the protocol and are not broader than the currently approved protocol unless justified |
| 5 | 884<br>B.I.e.4<br>Documentation | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or "confirmation" in the submission should be appropriate.<br>Documentation 1: propose "confirmation" instead of "declaration". | Documentation 1: [Delete: Declaration] Confirmation that the changes do not change the overall strategy defined in the post-approval change management protocol and are not broader than the currently approved protocol. |
| 6 | 885<br>B.I.e.5<br>Documentation 2 | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or "confirmation" in the submission should be appropriate. | Documentation 2: [Delete: Declaration] Confirmation that the change is in accordance with the approved post approval change management protocol and that the study results meet the acceptance criteria specified in the protocol. |

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| | | | Documentation 2: propose “confirmation” instead of “declaration”. | |
| 7 | 885<br>B.I.e.5 | EFPIA/VE | The proposal to allow flexibility with regard to classification of implementing variation is welcomed. Will complementing guidelines such as the Q&A on PACMP (EMA/CHMP/CVMP/QWP/586330/2010) be updated to reflect the additional flexibility for biological products proposed within the draft classification guideline? | We suggest that complementing guidelines such as the Q&A on PACMP (EMA/CHMP/CVMP/QWP/586330/2010) will be updated to reflect the additional flexibility for biological products proposed within the draft classification guideline. |
| 8 | 885<br>B.I.e.5 Note * | EFPIA/VE | The note* to documentation 2 is overly restrictive and prevents the applicant from presenting a justification for a minor difference during execution of the protocol. For example, when assessing statistical comparability for biological products which may have fallen outside an acceptance criteria depending on number of sample points included. Such examples could be addressed in an Implementation Q&A/ Update to the PACMP Q&A. Adopting an overly strict, generally non-flexible approach in the Variation Classification guideline risks driving an increase in higher classification variations and ultimately, a decrease in the uptake of PACMPs as a valuable regulatory tool. | [Delete: Note: *In case the acceptance criteria and / or other conditions in the protocol are not met, the change cannot be implemented as a variation of this category and should instead be submitted as variation of the applicable category without PACMP.] |
| 9 | 886<br>B.I.e.6 - Documentation 2 | EFPIA/VE | B.I.e.6 - Documentation 2: Introduction of PLCM is highly welcome, however the elements described in it may be too restrictive. It would be recommended to add “can include” | The product lifecycle management document can includes, but is not limited to a description of the material attributes, quality attributes and process parameters (or analytical procedure performance characteristics / analytical procedure parameters), their proposed limits |

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| | | | | and ranges, and future variation reporting categories, in a tabular format. |
| 10 | 887<br>B.I.e.7<br>Condition 2 | EFPIA/VE | Editorial amendment | 2. The change has been foreseen in the product lifecycle management document as a Type $IA_{\underline{IN}}$ variation requiring immediate notification following implementation |
| 11 | 887 | EFPIA/VE | Clarify process for introduction of an additional parameter or quality attribute to an approved PLCM. For example, it should be clarified that point d) “other changes” or B.II.g.6 should be used in this case. | B.I.e.7.d<br>Other changes to a process parameter or quality attribute (including addition)<br>Condition 3 (to be added): The change is not a result of unexpected events or out of specification results. Risk not considered major.<br>Documentation 1,2,3 |
| 12 | 887<br>B.I.e.7 | EFPIA/VE | B.I.e.7: the text only allows changes to attributes or parameters, while other changes (e.g., description) could also be covered by the PLCM. It is proposed to extend the scope to enable reporting of all changes that are described in the approved product lifecycle document. Point d) would cover moderate changes as well as unforeseen changes.<br>It would be important to illustrate the use of these variations in an implementation guide. | B.I.e.7 Changes to [Delete: process parameters or quality attributes related to the active substance as described in] an approved product lifecycle management document in relation to the active substance<br>a) Major changes in accordance with the approved product lifecycle management document<br>b) Minor changes in accordance with the approved product lifecycle management document |

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| | | | | c) Minor changes in accordance with the approved product lifecycle management document<br><br>d) Other changes in accordance with the approved product lifecycle management document, |
| 13 | 887<br>B.I.e.7 Documentation 2 | EFPIA/VE | B.I.e.7 Documentation 2: several submissions/changes may be reviewed/ongoing at a given time and the PLCM may not be fully correct at a given time depending on the order of approvals. It would therefore be recommended to limit the provisions in documentation 2 to an update of the PLCM to relevant sections being modified. | An updated product lifecycle management document of relevant sections being modified. [Delete: including updated description of the material attributes, quality attributes or process parameters (or analytical procedure parameters), as appropriate, their proposed limits and ranges, and future variation reporting categories, in tabular format.] |

**B.II Finished product**

***B.II.a) Description and composition***

| | Please insert reference to relevant scope or section *(e.g. B.II.a.1.a, Conditions, Documentation)* | Stakeholder name<br>*(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 888<br>General | EFPIA/VE | There are several change categories that do not appear commensurate with the potential risks related to certain changes. It is recommended that the below change types be revisited, considering risk and additional scientific considerations that | N/A |

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| | | | would merit a lower classification category. Specific examples are provided in the line items below (1) | |
| 2 | 888<br>B.II. FINISHED PRODUCT | EFPIA/VE | Consider whether it is redundant to repeat "finished product" throughout this section that is defined as "finished product". E.g. in B.II.b.1, B.II.b.2, B.II.b.3 (twice in one sentence), B.II.b.3 b), B.II.d.2, B.II.d.2 c), B.II.e.1 etc. | Consider deleting repetitions of 'finished product' |
| 3 | 892<br>B.II.a.3.b) 3 | EFPIA/VE | Conditions, documentation and procedure type missing for B.II.a.3 b) 3. Change that is supported by a bioequivalence study<br>Typographical error: Change is missing a classification | Add in an appropriate classification. |
| 4 | 892<br>B.II.a.3.b.2) | EFPIA/VE | The requirement to submit a Type II variation for any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk could be revised. This could be categorized as a Type 1B variation based on a science- and risk-based approach provided that there is no impact on the safety or quality of the product. | 2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product (including biological excipients [delete: or any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk])<br>5) Addition or replacement of an excipient for which an assessment is required of viral safety and/or TSE risk where there is no impact on the quality or safety of the medicinal product.<br>Procedure type: IB |
| 5 | 892+893 | EFPIA/VE | Condition 4 and documentation 3: Concepts from revision of ICH Q1 intending to clarify applicability | (…) at least two pilot or industrial scale batches, covering a minimum period of 3 months (…) |

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| | | | of requirements across development and lifecycle (risk-based approaches based on change) and ICH Q12 principles may be used to determine the need and extent of studies required to support changes. Therefore, alternative wording could be proposed. | Alternative scientifically justified approaches aligning with European and international scientific guidelines may be acceptable. |
| 6 | 892<br>B.II.a.3.b)1 | EFPIA/VE | 'Any minor adjustment of the quantitative composition of the finished product with respect to excipients'<br><br>Comment: remove condition 10 The product concerned is not a biological medicinal product<br><br>Rationale: the main risk of a minor change in excipient quantity for biological product is on stability or product quality, and this is already covered by condition 3.<br><br>Replace condition 10 by proposed wording. | Condition 10:<br>For biological products the changes do not impact the product quality, safety and efficacy. |
| 7 | 892<br>B.II.a.3.b)3. | EFPIA/VE | Change that is supported by a bioequivalence study would be removed as no condition nor deliverable are enclosed and it would be covered by B.II.a.3.b)2. | Remove B.II.a.3.b) 3<br><br>Change that is supported by a bioequivalence study |
| 8 | 892<br>B.II.a.3 | EFPIA/VE | Consider consistent approach with headings above subcategories, as in the updates to B.I.a.1 and B.I.b.2 | Change subcategory lettering and numbering to headings and lettering. |
| 9 | 892<br>B.II.a.3<br>And | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A | Documentation 2: Confirmation that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory |

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| | 893<br>B.II.a.4 | | statement or “confirmation” in the submission should be appropriate.<br><br>Documentation 2: propose confirmation instead of declaration. “A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).” | stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). |

***B.II.b) Manufacture***

| | Please insert reference to relevant scope or section *(e.g. B.II.a.1.a, Conditions, Documentation)* | Stakeholder name<br>*(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| **1** | | EFPIA/VE | There are several change categories where risk-based approach principles are not considered. For many of the changes related to manufacturing and testing of DS and DP the following condition is mentioned “The active substance/finished product | |

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| | General comment<br><br>897<br><br>B.II.b.1<br><br>Documentation 2, 4 & 8 | | is not a biological substance or sterile" or the number of batches required to support the change is restrictive for Bio products versus small molecules.<br><br>It is recommended to revise this condition, consider risk-based approaches and scientific knowledge focusing on the impact on Critical process parameters & or Critical quality attributes of the medicinal product.<br><br>Similarly, some variation categories are specific to Biological immunological medicinal products with higher reporting category for these changes regardless of the impact on the overall quality of the product which is not aligned with the risk based approach principle.<br><br>Some examples include:<br><br>Line 897 B.II.b.1:<br><br>For the addition/replacement of a Primary packaging site of non-sterile products, the number of batches (stated as "(>=3)" should be more flexible to allow technical or scientific rational.<br><br>In addition, this number is not aligned to the number of batches described in documentation 4:<br><br>4) Batch analysis data on one production batch and two pilot scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production | Line 897 B.II.b.1:<br><br>Recommend deleting new text and keeping previous guidance expectations for documentation 4:<br><br>"Batch analysis data on one production batch and two pilot scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).<br><br>[Delete: Batch analysis data of 3 batches (unless otherwise justified) of the biological |

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| | 900<br>B.II.b.3<br>Documentation 7 | | batches should be available on request or reported if outside specifications (with proposed action). Batch analysis data of 3 batches (unless otherwise justified) of the biological finished product, manufactured from the current and proposed manufacturers/sites.<br><br><u>Line 900 B.II.b.3, Documentation 7</u>:<br><br>For a minor change in manufacturing process, the requirement for 3 batches for biologicals should be more flexible to allow technical or scientific rational. | finished product, manufactured from the current and proposed manufacturers/sites.]<br><br>Documentation 2 should be revised accordingly:<br><br>"2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches [Delete: (≥3)] used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted."<br><br><u>Line 900 B.II.b.3, Documentation 7</u>:<br><br>"Batch analysis data (in a comparative tabulated format) on a minimum of 1 batch, [Delete: or 3 batches (unless otherwise justified) for biologicals,] manufactured to both the currently approved and the proposed process. Batch data on the next 2 full production batches should be made available on request and reported by the marketing authorisation holder if outside specification (with proposed action)." |
| 2 | 897 & 901<br>B.II.b.1.c & B.II.b.4 | EFPIA/VE | The clarification comment pertaining to the understanding between quality characteristics and in-vivo performance is misaligned with the inclusion | (*) Note: In change code B.II.b.1, a complex manufacturing processes is, amongst others, intended to cover situations where the link |

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| | Scope | | of continuous and decentralised manufacturing within the example list. For example, the link between CQA's of the oral solid dose products manufacture via continuous processes are well understood and decentralised manufacture may involve conventional manufacturing technology but at the point of care.<br><br>Furthermore, with the operation of the same process across different sites, it is expected that the knowledge and oversight of the process will be enhanced compared to standard manufacturing. As such, it is suggested to remove this reference in general.<br><br>It is recognised that novel manufacturing technology will for a time need to be considered complex but the relative experience and expertise of the MAH/Manufacturer will to a large extent drive the overall risk. Hence inclusion of specific examples within the clarifying statement is likely to preclude an appropriate risk based approach for these technologies and approaches in the future.<br><br>Lastly, this variation category footnote should clarify that the scope (i.e. complex manufacturing processes) does not include primary, secondary packaging, batch control testing/release. The updated category title and footnote are ambiguous on this point. | between quality characteristics and in-vivo performance is not fully understood. A complex manufacturing process could include the following scenarios (not exhaustive list); e.g. nanomedicines, ATMPs, liposomal formulations, lipid nanoparticles, [Delete: continuous manufacturing, decentralised manufacturing,] inhalation products. <u>It generally does not include primary, secondary packaging, batch control testing/release.</u> Where relevant, if a change is submitted as a type IB variation, it is up to the applicant to provide adequate justification for not considering a manufacturing process as a 'complex' one. However, under the safeguard clause, it should be noted that if the supplied justification is not accepted, it is possible for the competent authority to upgrade the submission to a type II variation. If unsure, applicants should consult the relevant competent authority before submitting the variation.<br><br>This comment applies to other categories where the same footnote is used e.g. line 901 b.II.b.4.d. |
| 3 | 897<br>B.II.b.1.f | EFPIA/VE | Currently the proposed wording for this category is open to interpretation that it refers to the assembly of a device. We suggest adding clarity of the category to make it clear that the category refers to | f) Addition or replacement of a site responsible for the final assembly of a finished product including an integral device (part). |

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| | | | assembly of the finished product including an integral medical device component.<br><br>Use “EMA/CHMP/QWP/BWP/259165/2019 Guideline on quality documentation for medicinal products when used with a medical device” terminology i.e. “integral medicinal products”.<br><br>If the device is integral, it should be referred to as a 'device' (part) instead of a medical device.<br><br>Clarify that it is final assembly of the iDDC – subassembly steps in device manufacturing should not be in scope | |
| 4 | 897 B.II.b.1,<br>900 B.II.b.3,<br>901 B.II.b.4 | EFPIA/VE | In general, the requirement to provide copies of approved documentation, to support variations e.g. provision of approved specifications is redundant, in light of submissions being made in eCTD format.<br><br>Remove requirement to provide unchanged information (Copy of approved release and end-of-shelf life specifications). | Remove documentation requirement to provide copies of approved information e.g. specifications:<br><br>[Delete: Copy of approved release and end-of-shelf life specifications if relevant.] |
| 5 | 899<br><br>B.II.b.2.a | EFPIA/VE | It should be made clear that all compendial methods should remain as IA changes.<br><br>Furthermore, Endotoxin testing is defined as a biological test method and would therefore be a type IB by default, even if it is in line with microbiological testing. Suggest to list endotoxin test in line with microbiological testing.<br><br>Lastly, include a cross-reference to EMQ post authorisation procedural advice (Q&A), 7.2.13. | Addition or replacement of a site where batch control/testing takes place applying <u>compendial and/or</u> physicochemical and/or microbiological <u>(incl endotoxins)</u> analytical procedures for the finished product. |

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| | B.II.b.2.b<br><br>B.II.b.2.c.2 and<br>B.II.b.2.c.3 | | If the methods concerned are compendial, the classification should be IA, managed under B.II.b.2.a.<br><br>Furthermore, there should be possibility to group a change of QC testing and/or release site with a change of analytical procedure (B.II.d.2.c) or without any change of analytical procedure.<br><br>If the methods concerned are compendial, the classification should be IAIN | Addition or replacement of a site where batch control/testing takes place applying a non-compendial biological/immunological/immunochemical analytical procedure for a biological finished product [Delete: (without change to analytical procedures).]<br><br>B.II.b.2.c.2 proposed text:<br><br>2) Including batch control/testing applying compendial and/or physicochemical and/or microbiological analytical procedures for the finished product<br><br>B.II.b.2.c.3 proposed text:<br><br>3) Including batch control/testing applying a non-compendial biological/immunological/immunochemical analytical procedure for a biological finished product [Delete: (without change to analytical procedures).] |

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| 6 | 898<br>B.II.b.1.f | EFPIA/VE | Change B.II.b.1.f Addition or replacement of a site responsible for the assembly of an integral medical device should be a type IAIN variation similarly to a secondary packaging site as all operation happen after primary packaging. | Allow for type IAIN variation for assembly transfer |
| 7 | 899<br>B.II.b.2<br>Documentation 5 | EFPIA/VE | Documentation 5 states that "depending on the variability of the specific method and the potential risk, to the quality, safety or efficacy of the product, posed by the proposed change, additional data such as a summary of the analytical procedure transfer test results may be required."<br><br>Suggest to revise Documentation 5. to requiring a declaration that test method transfer has been complete rather than providing the analytical procedure transfer protocols and potentially a summary of results. | Documentation 5:<br><br>A declaration by the Qualified Person (QP) responsible for batch certification stating that the test method transfer activities have been successfully completed. |
| 8 | 900<br>B.II.B.3 | EFPIA/VE | Typically, even for vaccine, one cumulative hold time lot was acceptable. Suggest revision of Documentation 10. | Documentation 10:<br><br>Data to validate the proposed change in holding time and/or storage condition of the intermediate or bulk product (minimum of [Delete: two] <u>one</u> batch[Delete:es] at pilot or commercial scale).<br><br>Qualitative and quantitative (if required) composition of the intermediate or bulk container should be described and its specification stated. |

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| | | | | If pilot scale batches are provided, a commitment to verify these data on commercial scale batches.<br><br>Declaration that the finished product shelf-life is set in accordance with the Note for guidance on start of shelf-life of the finished dosage form, or otherwise justified |
| 9 | 900<br>B.II.b.3.a<br>Document 9 | EFPIA/VE | There is already request in previous items for batch data and stability. A declaration does not seem to provide additional relevance beyond supporting data. | Propose removal of document 9. |
| 10 | 900<br>B.II.b.3<br>Documentation 8 | EFPIA/VE | Documentation 8:<br><br>Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or "confirmation" in the submission should be appropriate.<br><br>Suggest removing the constraints of 3 months stability data required at time of submission while keeping the commitment on stability. | Documentation 8:<br><br>[Delete: Declaration] Confirmation that relevant stability studies have been started under ICH conditions, as appropriate, (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch [Delete: and at least three months satisfactory stability data] are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action)." |

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| 11 | 900<br>B.II.b.3<br>Condition 7<br><br>Documentation 10 | EFPIA/VE<br><br><br><br><br><br><br><br><br><br><br><br>EFPIA/VE | Condition 7:<br>Suggest removing the constraints of 3 months stability data required at time of submission while keeping the commitment on stability, as related to minor changes which are not expected to impact quality and safety of the product.<br><br><br><br><br><br><br><br><br><br>Documentation 10:<br>Avoid misunderstanding by third countries and remove reference to the guidance as it would not cover sterile BioTech products. | Condition 7:<br>“7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch [Delete: and at least three months stability data are at the disposal of the applicant]. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action)”<br><br><br><br>Documentation 10:<br>“10. [Delete: Declaration] Confirmation that the shelf-life remains unchanged [Delete: finished product shelf-life is set in accordance with the Note for guidance on start of shelf-life of the finished dosage form, or otherwise justified.] |
| 12 | 901<br><br>B.II.b.4 a) | EFPIA/VE | B.II.b.4 a)<br>Take similar approach to DS, remove reference to 10-fold. Stay general and replace “Up to 10-fold increase compared to the originally approved batch size” by “An increase to the originally approved batch size” and remove condition 7. | B.II.b.4 a)<br>[Delete: “Up to 10-fold increase compared to the originally approved batch size] An increase to the approved batch size”<br><br>Condition 7<br>[Delete: Condition 7: The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.] |

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| | | | B.II.b.4.b)<br>Take similar approach to DS, remove reference to 10-fold. Stay General and replace “Downscaling down to 10-fold” by “Downscaling of the approved batch size” | B.II.b.4.b)<br>[Delete: “Downscaling to 10-fold] Downscaling of the approved batch size” |
| 13 | 901<br>B.II.b.4. | EFPIA/VE | B.II.b.4. f)<br>f) The scale for a biological medicinal product is increased / decreased without process change (e.g. duplication of line):<br><br>Considering that EMA post-authorisation procedural advice for users of the centralised procedure (Q&A) 7.2.9: “What changes in manufacturing sites, buildings and rooms are covered by the company Quality Assurance System (GMP)? Rev. May 2018” states that a new filing line identical to an already approved one in an authorised room, building, manufacturing site does not require a variation, there is ambiguity over what does and does not require a variation.<br><br>Furthermore, there could be minor changes in batch size, where a comparability assessment would be performed, but the change has a low risk for product quality impact. The possibility for Type IB changes could provide industry and the HA assessors with resource savings for such low risk changes. | B.II.b.4. f)<br>f) The scale for a biological medicinal product is increased / decreased without process change [Delete: (e.g. duplication of line)] or without significant impact on the quality, safety or efficacy of the medicinal product. |
| 14 | 901<br><br>B.II.b.4, | EFPIA/VE | Regarding condition 5 for changes a and b related to batch size and change f: this condition precludes biological product batch size changes from being | [Delete: 5. The product concerned is not a biological medicinal product (refer to category c or f).] |

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| | Conditions 5 | | reported through a Type 1A reporting mechanism. DP manufacturing processes for biologics are not inherently more complicated than small molecules, and often consist only of filling a liquid into a container. Batch size changes should be able to be reported through a Type 1A mechanism. | |
| 15 | 901<br>B.II.b.4; Documentation 2 | EFPIA/VE | Documentation 2<br>There should not be a general requirement to provide more comparative batch analysis data for biologics compared to small molecules. It should be based on a risk assessment. There should also be an option to provide only one batch as in current guideline and therefore or "unless otherwise justified" is added. | Documentation 2<br>"2. Batch analysis data (in a comparative tabulated format) on a minimum of one [Delete: two] production batches of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes, [Delete: Batch analysis data of 3 batches] (unless otherwise justified) [Delete: for biological active substance, should be available for the proposed batch size]. |
| 16 | 901<br>B.II.b.4.f<br>Documentation 6 | EFPIA/VE | Documentation 6:<br>Suggest to remove the constraints of 3 months stability data required at time of submission while keeping the commitment on stability.<br><br>Concepts from revision of ICH Q1 intending to clarify applicability of requirements across development and lifecycle (risk-based approaches based on change) may be used to determine the need and extent of studies required to support changes. Therefore, alternative wording could be proposed. | Documentation 6:<br>"6. The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch [Delete:, covering a minimum period of 3 months,] and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). Alternative scientifically justified approaches aligning with |

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| | | | | European and international scientific guidelines may be acceptable. |
| 17 | 902<br>B.II.b.5.g | EFPIA/VE | A replacement of a non-critical or equivalent test procedure should be possible under a Type IA. Thus, reporting category should be risk-based and connected with a condition for Type IA that the procedure is even better. If this condition is not fulfilled, change would be classified as Type IB by default. In addition, it should be clarified that this change category also refers to the corresponding test procedure. | Replacement of an in-process test and/or analytical procedure (Type 1A variation).<br>Additional condition to be fulfilled:<br>The new in-process test and/or analytical procedure exceeds previous method capabilities and provides an increased control or does not refer to a critical IPC. |
| 18 | 902<br>B.II.b.5<br>Condition 7 | EFPIA/VE | For condition 7 there is unclarity about the listed critical attribute “assay”. In any case, as this listing leads to unclarity and too many restrictions as to what is critical or not which should be based on the company’s risk assessment and thus proposed to be deleted. | 7. The in-process test does not concern a critical attribute not otherwise monitored. [Delete: for example:<br>• assay<br>• purity,<br>• impurities (except when a solvent is no longer used in the manufacture of the active substance),<br>• a critical physical characteristic (for example: particle size, bulk or tapped density),<br>• identity test,<br>• or water content.] |
| 19 | 902<br>B.II.b.5, Documentation 4 | EFPIA/VE | Batch analysis data should not be required for a change to an IPC test under category B.II.b.5 b) and g). To support the adequacy of an added or replaced IPC test, data should be provided showing the new method is capable of monitoring the attributes to | “4. Documentation that new test is an adequate in-process control including (as appropriate) batch analysis data on two production batches [Delete: Batch analysis data on two production batches [(3 production |

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| | | | the same or better extent as the current method. Thus documentation (data/justification) for this should be provided rather than batch analysis data. Of course, if deemed necessary it could be complemented by batch analysis data but it should not be standard requirement. In addition, there should not be a different requirement for biologics per se but also risk-based. | batches (unless otherwise justified) for biologicals]) of the finished product for all specification parameters.] of the finished product for all specification parameters." |
| 20 | 902<br>B.II.b.5<br>Documentation Note | EFPIA/VE | To delete the note: in contradiction with item c. | [Delete: "Note: This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate."] |

***B.II.c) Control of excipients***

| | Please insert reference to relevant scope or section *(e.g. B.II.a.1.a, Conditions, Documentation)* | Stakeholder name<br>*(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 903 (& 906)<br>General (& B.II.c.3.b) | EFPIA/VE | There are several change categories that do not appear commensurate with the potential risks related to certain changes. It is recommended that the below change types be revisited, considering risk and additional scientific considerations that would merit a lower classification category. A specific example is provided below:<br>Category B.II.c.3.b: The requirement to submit a Type II variation for a "Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability" could be revised. This could be categorized as a Type 1B variation based on a science- and risk-based approach provided that there is no impact on the safety or quality of the product. | Propose to update B.II.c.3.b) as follows:<br>Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability where there is no impact on the quality or safety of the product.<br>Procedure type: IB<br>Propose new associated document:<br>Document 3: TSE Risk evaluation of the new TSE material or the TSE risk material from the new TSE risk material supplier. |
| 2 | 904<br>B.II.c.I.b), f), g)<br>Document 4 | EFPIA/VE | A risk based approach in relation to the supporting data should be adopted.<br>A requirement for supporting batch analysis from three batches should be reserved for higher risk excipients e.g. novel or critical, rather than a blanket application for biological excipients.<br>In all other cases, it should be possible to justify provision of batch analysis from a single batch of excipient, especially in the case of moving from in house specification to a compendial under change (B.II.c.1.f.) | Propose to update Document 4 as follows:<br>Batch analysis data (unless otherwise justified and/or substituted) on one production batch [3 production batches (unless otherwise justified) for critical or novel excipients] of the excipient for all specification parameters. |
| 3 | 904 | EFPIA/VE | There may sometimes be multiple IPCs that test the same critical attribute. Therefore, an IPC | Propose to update text as follows: |

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| | B.II.c.1<br>Condition 7 | | should be permitted to be removed, if another IPC remains that tests that same critical attribute.<br><br>Additionally, there is a lack of clarity regarding the listed critical attribute “assay”. What is critical should be based on the company’s risk assessment. Recommendation to remove all examples. | Condition 7: The in-process test does not concern a critical attribute not otherwise monitored. |
| 4 | 904<br>B.II.c.1<br>Document Note | EFPIA/VE | Propose to delete the note since the asterix (*) isn't associated with any text, and is in contradiction with item c. | Propose to delete the Document Note. |
| 5 | 904<br>B.II.c.1.f) | EFPIA/VE | Propose to add clarity to change from in-house specification to a pharmacopoeial monograph rather than the change of a single attribute. | Propose to update B.II.c.1.f) as follows:<br>Change from in-house specifications for the excipient to the monograph of a non-official Pharmacopoeia or a Pharmacopoeia of a third country where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State. |
| 6 | 904<br>B.II.c.1<br>Conditions 1& 3 | EFPIA/VE | Typographical error:<br>“chriteria” is used throughout the text, but is spelt incorrectly. | Propose to correct typographical error in Conditions 1 and 3 as follows:<br>criteria |

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| 7 | 905<br>B.II.c.2<br>Condition 4 | EFPIA/VE | Condition 4 should be deleted from list of conditions because it is no longer referenced as a condition to be fulfilled. | Propose to delete Condition 4. |
| 8 | 906<br>B.II.c.3.a) | EFPIA/VE | Change B.II.c.3.a)1 allows for reporting a change from a TSE risk material to non-animal derived products through a Type IA reporting mechanism.<br>Change B.II.c.3.a)2 requires biologics to submit this change as a Type 1B.<br>Changing from an animal derived raw material to a non-animal derived raw material is not inherently riskier for a biologics and is considered an improvement in the process. Biological products should be able to report this type of change through a Type 1A mechanism. | Propose to update B.II.c.3.a as follows:<br>"a) From TSE risk material to vegetable or synthetic origin for excipients or reagents used in a manufacture of a medicinal product.<br>Procedure Type: IA |
| 9 | 906<br>B.II.c.3<br>Document 1 | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance) the terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or "confirmation" in the submission should be appropriate. | Propose to update Document 1 as follows:<br>Confirmation from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin." |
| 10 | 907<br>B.II.c.4<br>Document 4 | EFPIA/VE | As per eCTD format, unchanged documents cannot be submitted again, hence it does not make sense to request a copy of the approved specification that is already part of the eCTD. Propose to delete this requirement. | Propose to update Document 4 as follows:<br>Copy of new specifications of the excipient (if applicable). |

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| 11 | 907<br>B.II.c.4 d) | EFPIA/VE | The description of B.II.c.4.d) is not clear. | Propose to update B.II.c.4.d) as follows:<br>Addition or replacement of a site responsible for the manufacture or testing of an excipient when described in the dossier |
| 12 | 907<br>B.II.c.4. a) and d)<br>Document 2 | EFPIA/VE | A risk based approach in relation to the supporting data should be adopted, with the number of required batch analysis data scientifically justified. It should be possible to justify provision of batch analysis from a single batch of excipient. | Propose to update Document 2 as follows:<br>Batch analysis data (in a comparative tabulated format) of at least one batch (minimum pilot scale) of the excipient manufactured according to the present and proposed process, or by the present and proposed manufacturer, as applicable. |

***B.II.d) Control of finished product***

| | Please insert reference to relevant scope or section *(e.g. B.II.a.1.a, Conditions, Documentation)* | Stakeholder name<br>*(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 908<br>Condition 6 | EFPIA/VE | Condition 6: The addition of a specification for a genotoxic impurity at any point of control would be submitted as a Type IB and subject to assessment due to the condition 2. As such, the wording of condition 6 is somewhat superfluous and creates ambiguity over whether other parts of an impurity control strategy (e.g. addition of other specification | Propose to update Condition 6 as follows:<br>Condition 6: The change does not concern dissolution. |

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| | | | attributes) can be submitted as a Type IA or Type IB. Propose to remove reference to impurities from the condition. | |
| 2 | 909<br>B.II.d.1 a) and b) | EFPIA/VE | General comment: It is recommended to use consistent language across the different sections of the variation guideline.<br>As an example B.I.b.1.a) and b) state "Change within the approved specification acceptance criteria….."<br>Whereas B.II.d.1.a) and b) stated "Change within the specification acceptance criteria....." | Propose to update B.II.d.1.a) and b) as follows:<br>Change within the approved specification acceptance criteria……<br>Propose consistent use of language throughout the document. |
| 3 | 909 & 910<br>B.II.d.1 & B.II.d.2 | EFPIA/VE | Diluents (for example WFI) are simple drug products and may be reported under lower reporting categories using a risk-based approach. | Recommend including specific codes for changes impacting diluents that have lower reporting categories. |
| 4 | 909<br>B.II.d.1<br>Document 4 & 7 | EFPIA/VE | There is no value in commercial batch data of drug product for which specifications have been altered. For the most part the respective analytical method validation status is more appropriate. This might not be the case for changes that may have significant impact where commercial batch data may be reasonably anticipated but proposals for reduced commercial batch data in that circumstance could even be proposed. A risk based scientific approach for minor changes should be facilitated utilising historical /development / characterisation / method validation data in the context of justifying the continued applicability / relevance of the control strategy. Propose Document 4 to be removed from all minor variation categories and Document 7 amended. | Propose to update the text as follows:<br>Delete Documentation 4.<br>Update Documentation 7: Justification that with the change, the control strategy remains suitable for the purpose of controlling product quality. |

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| 5 | 909<br>B.II.d.1 | EFPIA/VE | There is no change category provided to update the dossier in line with a Ph. Eur drug product monograph in either B.II.d.1 or B.III sections. | Propose to update B.II.d.1.g) as follows:<br><br>Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur (2) or of an updated monograph on a medicinal product of the Ph. Eur or national pharmacopoeia of a Member State. |
| 6 | 909<br>B.II.d.1.g)<br>Condition 7 | EFPIA/VE | Condition 7 for change B.II.d.1.g effectively makes this a specific change for microbial methods. However, it should be possible to introduce changes to other general monographs.<br>In addition, the rationale for B.II.d.1.g as a type IAIN v's B.II.d.1.h as a type IA is unclear. Both changes propose to update in line with the Ph. Eur. hence should be viewed as a similar risk. | Propose to update B.II.d.1.g) as follows:<br>Classification: IA<br>Propose to update condition 7 as follows:<br>If the change is concerning the updating of the microbial control acceptance criteria to be in line with the current Pharmacopoeia, and the currently registered microbial control acceptance criteria (present situation) are in line with the pre January 2008 (non harmonised) situation, the proposed controls are in line with the harmonised monograph for the particular dosage form without any additional specified controls over the Pharmacopoeia requirements. |
| 7 | 909<br>B.II.d.1<br>Condition 8 | EFPIA/VE | There may sometimes be multiple specification attributes that test the same critical attribute. Therefore, a specification attribute should be permitted to be removed, if another specification | Propose to update text as follows:<br><br>Condition 8: The specification parameter attribute or proposal for the specific dosage form does not |

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| | | | attribute remains that tests that same critical attribute.<br><br>Additionally there is a lack of clarity regarding the listed critical attribute “assay”. What is critical should be based on the company’s risk assessment. Recommendation to remove all examples | concern a critical attribute not otherwise monitored.<br><br>Note 1. This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled using science and risk-based approaches when defining the reporting category. |
| 8 | 909<br>B.II.d.1.e | EFPIA/VE | B.II.d.1.e) currently presents a high regulatory burden where limits were initially established based on fewer data and set conservatively and could be reasonably foreseen as a Type IB. This could act as an impediment to the concept of patient centric / clinically relevant specification setting and an impediment to revision to ICH Q6 concepts.<br><br>Propose to expand B.II.d.1.e) to cover where there may be significant impact to the overall quality of the finished product.<br><br>In addition propose the creation of another category between the current e) and f) categories that covers when there is no significant impact to the overall quality of the finished product. | Propose to update the text as follows:<br><br>e) Change outside of the approved specification acceptance criteria of the finished product, which may have a significant effect on the overall quality of the finished product<br><br>INTRODUCTION OF AN ADDITIONAL CHANGE CATEGORY:<br><br>Change outside of the approved specification acceptance criteria for the finished product where there is no significant impact on the overall quality of the finished product<br><br>Procedure Type: IB |

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| | | | | Documents to be supplied: 1, 2, 4, 7 |
| 9 | 910<br>B.II.d.2<br>Condition 4 | EFPIA/VE | It is unclear why either change requiring condition 4 (deletion of a method where an alternative is registered B.II.d.2.b or update of an analytical method to comply with an updated general monograph in Ph. Eur B.II.d.2.e) requires distinction between chemical and biological/immunological/immunochemical analytical procedures hence it is proposed to delete condition 4 from B.II.d.2. | Propose to update text as follows:<br>Delete Condition 4. |
| 10 | 910<br>B.II.d.2.c. | EFPIA/VE | It is not clear why a type II variation would be required if a Ph. Eur method was introduced. This category should only be for non-compendial methods hence a new change category is proposed relating to Ph. Eur. | Propose to update the text as follows:<br>INTRODUCTION OF AN ADDITIONAL CHANGE CATEGORY:<br>Introduction or replacement with a biological/immunological/immunochemical analytical procedure to comply with the European Pharmacopoeia or the national pharmacopoeia of a member state.<br>Procedure Type: IA<br>Conditions: 1<br>Documents to be supplied: 1,2 |
| 11 | 910<br>B.II.d.2 | EFPIA/VE | Recommend that the addition of a test to further control product quality is a Type 1A. | Propose to update the text as follows:<br>INTRODUCTION OF AN ADDITIONAL CHANGE CATEGORY:<br>Introduction of an additional analytical method to control an existing specification attribute. |

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| | | | | Procedure Type: IA<br><br>Conditions:<br><br>1. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.<br>2. The change does not result from unexpected events arising during manufacture or as a result of a safety or quality issue, e.g. new unqualified impurity; change in total impurity acceptance criteria.<br><br>Documents to be supplied: 1, 2 |
| 12 | 910<br><br>B.II.d.2.c | EFPIA/VE | B.II.d.1.c provides for the addition of a new specification test with its corresponding method with condition 5 based around the use of novel analytical methods or standard techniques in a novel way. Propose to align the terminology and remove the discrimination against biological/immunological/immunochemical methods by altering the wording of the change category. | Propose to update the text as follows:<br><br>c) Introduction, Replacement, or Substantial change to an analytical procedure containing a novel non-standard technique or a standard technique used in a novel way. |
| 13 | 910<br><br>B.II.d.2.e | EFPIA/VE | There is no change category provided to update the registered analytical methods in line with a Ph. Eur drug product monograph either in B.II.d.2 or B.III sections. | Propose to update B.II.d.2.e) as follows:<br><br>Update of the analytical procedure to comply with the provisions of an updated general monograph of the Ph. Eur or of an updated monograph on a medicinal product of the Ph. Eur or national pharmacopoeia of a Member State. |
| 14 | 911 | EFPIA/VE | RTRT proposal as it is currently proposed is not considered granular enough and consequently adds | Propose to update the text as follows: |

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| | B.II.d.3 | | additional regulatory burden. This change should be further granulated. | B.II.d.3 Variations related to real -time release testing in the manufacture of the finished product<br><br>a) Introduction or major changes to RTRT<br>Procedure Type: II<br><br>b) Minor changes to approved RTRT<br>Procedure Type: IB<br>Document to be supplied:1, 2<br>1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data (if applicable)<br>2. Justification that the minor change has no impact on the overall control strategy of the Drug Product. |

***B.II.e) Container closure system***

| | Please insert reference to relevant scope or section *(e.g.* | Stakeholder name<br>*(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| | *B.II.a.1.a, Conditions, Documentation)* | | | |
| 1 | 913<br>B.II.e.1<br>Change in container closure composition | EFPIA/VE | Change to equivalent packaging requires 2 batches, 3m real time ICH stability data before implementation. Similar to comment on DS (B.I.c.1.a). No consideration given to whether modelling or historic/Platform dataset for a product could be used to reduce the stability requirements. | Classification to remain as type 1A but consider revision to ICH Q1 and whether for products where stability is fully understood that 2 batches of ICH stability data is proportionate if material is demonstrated to be equivalent. |
| 2 | 913<br>B.II.e.1.a) 3 & B.II.e.1.b).2 | EFPIA/VE | Flexibility should be added e.g. Type IB when there are like for like changes. The default for all should not be Type II. | Create an additional type IB change code<br>5. The change is functionally like-for-like, providing comparable protection<br>Procedure Type – IB<br>Conditions: 1, 2<br>Documentation: 1, 2 |
| 3 | 913<br>B.II.e.1<br>Condition 3<br>Documentation 5<br>+<br>914<br>B.II.e.2<br>Documentation 3 | EFPIA/VE | Condition 3 and Documentation 5: Concepts from revision of ICH Q1 intending to clarify applicability of requirements across development and lifecycle (risk-based approaches based on change) and ICH Q12 principles may be used to determine the need and extent of studies required to support changes. Therefore, alternative wording could be proposed. | Remove the constraints of 3 months stability data required at time of submission while keeping the commitment on stability to expedite life cycle management (ICHQ12)<br>e.g for change B.II.e.1 (…) at least two pilot or industrial scale batches, covering a minimum period of 3 months (…) Alternative scientifically justified approaches aligning with European and international scientific guidelines may be acceptable. |

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| 4 | 913<br>B.II.e.1<br>Documentation 4<br>+<br>918<br>B.II.e.6<br>Documentation 6 | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology “declaration” could be perceived as a separate signed document therefore increasing documentation burden and proliferation. A statement or “confirmation” in the submission should be appropriate. | Replace “declaration” by “confirmation”. |
| 5 | 913<br>B.II.e.1 | EFPIA/VE | Consider including specific codes for changes impacting diluents.<br><br>Rationale: diluents (for example WFI) are simple drug products and may be reported under lower reporting categories using a risk-based approach. | Change in immediate packaging of the finished product<br>Proposal to include diluents:<br>a) 5. The change refers to the packaging of the diluent-Category IB<br>Conditions: None<br>Documentation: Batch data from 2 representative diluent batches; stability for one representative batch to be started, and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).<br>b) 4. The change refers to the container of the diluent-Category IB<br>Conditions: None |

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| | | | | Documentation: Batch data from 2 representative diluent batches; stability for one representative batch to be started, and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). |
| 6 | 914 | EFPIA/VE | Condition 3 and Documentation 3: Concepts from revision of ICH Q1 intending to clarify applicability of requirements across development and lifecycle (risk-based approaches based on change) and ICH Q12 principles may be used to determine the need and extent of studies required to support changes. Therefore, alternative wording could be proposed. | (…) at least one pilot or industrial scale batch, covering a minimum period of 3 months (…) Alternative scientifically justified approaches aligning with European and international scientific guidelines may be acceptable. |
| 7 | 914<br>B.II.e.2 | EFPIA/VE | Please clarify whether this section refers to the CCS of the finished product only or also to the bulk drug product | Change in shape or dimension of the container or closure (immediate packaging) of the finished product. |
| 8 | 915<br>B.II.e.3 | EFPIA/VE | Change in any part of the (primary) packaging material": Would be helpful to have clarification whether this excludes the secondary packaging material or might also include. What about changes in dimensions or material of secondary packaging: Out of scope? What about changes in the blister configuration? RO HA requests a B.II.e.6 Change in pack size for a switch of 3x10 to 1x30 tablets, which is rather B.II.e.2 Change in dimensions of the container. | N/A |

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| 9 | 916<br>B.II.e.4<br><br>917<br>B.II.e.5 | EFPIA/VE | Clarify that those changes also apply to diluents. | Change in the specification attribute and/or acceptance criteria of the immediate packaging of the finished product (including diluents). |
| 10 | 916<br>B.II.e.4<br>Note | EFPIA/VE | The reference (*) should be assigned to at least one of the changes under category B.II.e.4, so make clear to which category the “Note” belongs to. Otherwise asterisk to be deleted. | (*) has to be included where applicable |
| 11 | 918<br>B.II.e.6 | EFPIA/VE | The introduction of a new pack size (i.e. in addition to currently approved pack sizes) should be submitted as a variation under scope B.II.e.6 in line with EMA Q&A 2.6 | a. Introduction of a new pack siz**e** or change in the number of units (e.g. tablets, ampoules, etc.) in a pack<br>1. Change is within the range of the currently approved pack sizes<br>2. Change outside the range of the currently approved pack sizes |
| 12 | 918<br>B.II.e.6.c)<br>B.II.e.6.d) | EFPIA/VE | It is unclear why changes to fill weight/fill volume is classified under change of pack size, unless it covers a multidose modified to contain an increased number of doses. | Consider moving to B.II.a or B.II.b.3<br>If it covers a multidose modified to contain an increased number of doses, reformulate. |
| 13 | 918<br>B.II.e.6 | EFPIA/VE | Note at end of table refers to B.II.e.5 c) and d). | Change to<br>B.II.e.6 c) and d) |
| 14 | 919<br>B.II.e.7 Document 4 | EFPIA/VE | Typo “releavant” misspelled. | Change to “relevant” |

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| 15 | 919<br>B.II.e.7 | EFPIA/VE | Propose to add C – change to the sterilisation process without any impact to validated process. | B.II.e.7<br>C - change to the sterilisation process without any impact to validated process<br><br>Proposed category: Type IA<br>Conditions: 1,2,3,4<br>Documents: 1 |
| 16 | 920<br>B.II.e.8 | EFPIA/VE | Some dossiers mention "... blister in a folding box." Does this qualify/require the submission of a variation when changing the dimensions or material of the folding box. Or only in case of a more detailed description of the folding box and/or its size and/or its material? | When secondary packaging dimensions are not described in module 3, but the position of the text of the artwork is changed due to a packaging dimension change, guidance is requested on whether or not there should be a variation. |
| 17 | 920<br>B.II.e.8 | EFPIA/VE | Secondary packaging components, where described, that do not play a functional role, will not impact Quality of the product and therefore should not be subject to variation. This information can be regarded as supportive and managed in Company's PQS (Pharmaceutical Quality System) based on a risk assessment. The relevant sections can be updated at next occasion to avoid unnecessary challenges to supply continuity in EU and reliant markets. | B.II.e.8 Condition 1:<br>The secondary packaging [delete text] is not less protective than the approved one. |

***B.II.f) Stability***

| | Please insert reference to relevant scope or section *(e.g. B.II.a.1.a, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 922<br>B.II.f.1.(b) | EFPIA/VE | The classification as written does not offer a defined change code for the extension of the shelf life of biological products supported by real time data. Condition 4 excludes biologics and is inconsistent with the approach adopted for a similar drug substance change [B.I.d.1.(a)].<br>It is considered entirely appropriate for Type $IA_{IN}$ to apply to a biologic shelf-life extension when the real-time data support and there is no change in trends (Condition 3). This risk is no different than for a small molecule.<br>Condition 5 suggests that the category only applies to IR tablets and leaves biologics without a shelf-life extension category when supported by real-time data. | Consider removing condition 4 and 5 from B.II.f.1.(b).1<br>Condition 4: [delete text]<br>Condition 5: [delete text] |
| 2 | 922<br>B.II.f.1<br>Documentation | EFPIA/VE | As with the eCTD unchanged documents cannot be submitted again, it does not make sense to request a copy of the approved specification that is already part of the eCTD. Therefore, it is proposed to delete this requirement. | Documentation 3: [delete text] |

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| | | | This approach should be added to all change categories that require a copy of the approved specification:<br>B.I.a.2: Documentation 3<br>B.I.a.3: Documentation 4<br>B.I.d.1: Documentation 3<br>B.I.e.5: Documentation 5<br>B.II.b: Documentation 4<br>B.II.b.3: Documentation 6<br>B.II.b.4: Documentation 3 | |
| 3 | 922<br>B.II.f.1 Documentation | EFPIA/VE | It is unnecessary to state or increase the expectation to "3 batches (unless otherwise justified)" for biologicals and should be deleted.<br>ICH Q1 current and revision (Tier 1 guideline) would state the number of batches for post-approval changes and for 'in-use' (after opening) on an appropriate science & risk basis.<br>Increasing the burden for biologicals risks could result in contradiction with ICH guidance. | 1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format. This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on at least two, unless otherwise justified [delete text] pilot scale batches (1) of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate. Where applicable, results of appropriate microbiological testing should be included. |
| 4 | 922<br>B.II.f.1, Condition 5 | EFPIA/VE | Product is an immediate release film-coated tablets. | Propose to delete this condition and not limit this opportunity to IR tablets only. |
| 5 | 922 | EFPIA/VE | Change B.II.f.1.b.5: would this change category also cover use of modelling for shelf-life extension | |

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| | | | of FP after ICH Q1 revision is implemented? If this is the case, since the ICH Q1 revision is very likely to include modelling. Change B.II.f.1.4 would become obsolete after ICH Q1 revision implementation.<br><br>It is assumed the intent is to have a distinction between extrapolation (small molecules per current ICH Q1E decision tree) and stability modelling. This is confusing since extrapolation is achieved through a form of modelling even if statistically derived or inferred from accelerated conditions data.<br><br>If this assumption is correct then the guideline needs to explain.<br><br>The proposed edit assumes Type II variation for extrapolation not in accordance to guidelines and Type II variation for stability modelling. | An explanation of 'extrapolation' versus 'stability modelling' is critical. |
| 6 | 922<br><br>B.II.f.1.b)1 | EFPIA/VE | Suggest to delete "in line with stability protocol" as it is already part of condition 3. | As packaged for sale (supported by real time data [delete text]. |
| 7 | 922<br><br>B.II.f.1.b)5 | EFPIA/VE | Subcategory and Condition should be adapted for both real time data and extrapolation (including modelling) in line with latest ICH Q1 guideline. | Extension of the shelf-life of a finished product based on real time or extrapolation or modelling of stability data in accordance with relevant stability guidelines protocol for small molecule. |

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| | | | | Add clearly that the intent is for small molecules only. |

***B.II.g) Additional regulatory tools***

| | Please insert reference to relevant scope or section *(e.g. B.II.a.1.a, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 924<br>B.II.g.1<br>Conditions | EFPIA/VE | B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product<br>No conditions are specified in this category with assessment of Type IB. Changes to the approved design space ("c") may cause change to the performance and ability of the device part to safely and effectively deliver the final product. Such changes could also trigger additional reportable device changes to design, usability, performance, material, or specifications. This condition of change may not be appropriate under a Type IB category. | B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product<br>Add condition to be applied to changes under B.II.G.1.c:<br>Change to final product when used with an integral device (part) does not have a significant impact on its performance, delivery, quality, safety or efficacy. |
| 2 | B.II.g.1 b) | EFPIA/VE | B.I.e.1 b) introduces MODR which is appreciated. However, the reporting type appears to be disproportionate compared to the risk level as MODR would only enable some changes for a given analytical technology. | It would be recommended to have a specific category for introduction or extension of a MODR as a type IB to encourage enhanced analytical development. |
| 3 | 927<br>B.II.g.4 | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The | Documentation 1: "[Delete: Declaration] Confirmation that the changes do not |

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| | Documentation 1 | | terminology “declaration” could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or “confirmation” in the submission should be appropriate.<br><br>Documentation 1: replace “declaration” by “confirmation”. | change the overall strategy defined in the protocol and are not broader than the currently approved protocol.” |
| 4 | 928<br>B.II.g.5<br>Documentation 2 | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology “declaration” could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or “confirmation” in the submission should be appropriate.<br><br>Documentation 2: replace “declaration” by “confirmation”. | Documentation 2: “[Delete: Declaration] Confirmation that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol.” |
| 5 | 928<br>B.II.g.5<br>Note * | EFPIA/VE | The note* to documentation 2 is overly restrictive and prevents the applicant from presenting a justification for a minor difference during execution of the protocol. For example, when assessing statistical comparability for biological products which may have fallen outside an acceptance criterion depending on number of sample points included. Such examples could be addressed in an Implementation Q&A/ Update to the PACMP Q&A. Adopting an overly strict, generally non-flexible approach in the Variation Classification guideline risks driving an increase in higher classification variations and ultimately, a | Delete [Note: *In case the acceptance criteria and / or other conditions in the protocol are not met, the change cannot be implemented as a variation of this category and should instead be submitted as variation of the applicable category without PACMP.] |

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| | | | decrease in the uptake of PACMPs as a valuable regulatory tool. | |
| 6 | 929<br>B.II.g.6 - Documentation 2 | EFPIA/VE | B.II.g.6 - Documentation 2: Introduction of PLCM is highly welcome, however the element described in may be too restrictive. It would be recommended to add “can include”. | The product lifecycle management document can include~~s~~ a description of the material attributes, quality attributes and process parameters (or analytical procedure parameters), their proposed limits and ranges, and future variation reporting categories, in a tabular format. |
| 7 | 930<br>B.II.g.7.d | EFPIA/VE | Clarify process for introduction of an additional parameter or quality attribute to an approved PLCM. For example, it should be clarified that point d) “other changes” or B.II.g.6 should be used in this case. | B.II.g.7 d<br>Other changes to a process parameter or quality attribute (including addition)<br>Condition 3 (to be added): The change is not a result of unexpected events or out of specification results. Risk not considered major.<br>Documentation 1,2,3 |
| 8 | 930<br>B.II.g.7 | EFPIA/VE | B.II.g.7: the text only allows changes to attributes or parameters, while other changes (e.g., description) could also be covered by the PLCM. It is proposed to extend the scope to enable reporting of all changes that are described in the approved product lifecycle document. Point d) would cover moderate changes as well as unforeseen changes.<br>It would be important to illustrate the use of these variations in an implementation guide. | B.II.g.7 Changes [Delete: to process parameters or quality attributes] related to the finished product as described in an approved product lifecycle management document<br>“a) Major changes in accordance with the approved product lifecycle management document |

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| | | | | b) Minor changes in accordance with the approved product lifecycle management document<br><br>c) Minor changes in accordance with the approved product lifecycle management document<br><br>d) Other changes in accordance with the approved product lifecycle management document. |
| 9 | 930<br><br>B.II.g.7 Documentation 2 | EFPIA/VE | B.II.g.7 Documentation 2: several submissions/changes may be reviewed/ongoing at a given time and the PLCM may not be fully correct at a given time depending on the order of approvals. It would therefore be recommended to limit the provisions in documentation 2 to an update of the PLCM to relevant sections being modified. | An updated product lifecycle management document of relevant sections being modified.<br>[Delete: including updated description of the material attributes, quality attributes or process parameters (or analytical procedure parameters), as appropriate, their proposed limits and ranges, and future variation reporting categories, in tabular format.] |

***B.II.h) Adventitious Agents Safety***

| | Please insert reference to relevant scope or section *(e.g. B.II.a.1.a, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 931<br>B.II.h.1 | EFPIA/VE | Point b) 1. Modification of the risk assessment may not always lead to a higher risk taking, and as such a default type II for all modifications could be lowered in some situations. It would be recommended to modify B.II.h.1 b) 2. to enable updates of the risk assessment that would lead to equivalent or lower risk taking. | b) 2. without modification of risk assessment, or resulting in equivalent or lower risk taking. |

**B.III CEP/TSE/monographs**

| | Please insert reference to relevant scope or section *(e.g. B.III.1.a, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | 934<br>B.III.1 | EFPIA/VE | Text proposal to ease the wording. | B.III.1 Submission of a new or updated CEP or deletion of CEP. |

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| | | | | The same to be applied to the below text in section B.III.1. |
| 2 | 934<br>B.III.1<br>Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:<br>- For an active substance<br>- For a starting material/reagent/intermediate used in the manufacturing process of the active substance<br>- For an excipient | EFPIA/VE | Not all requirements are listed under documentation 2. It is suggested to include references to Q&A QWP Questions and Answers (Q&A): how to use a CEP in the context of a Marketing Authorisation Application (MAA) or a Marketing Authorisation Variation (MAV) or alternatively refer to a section V references where all appropriate information will be provided (see other comments).<br><br>See 'other comments' is referencing the 'Other Comments' section, in particular comment #3 starting with:<br>Currently the applicants need to consult several documents to make sure they have all the correct information... | More information on the requirements can be found in Q&A QWP Questions and Answers (Q&A): how to use a CEP in the context of a Marketing Authorisation Application (MAA) or a Marketing Authorisation Variation (MAV), see section V 'References'. |
| 3 | 934<br>B.III.1.a.1<br>Condition 1 | EFPIA/VE | Condition 1 states 'The impact […], on the finished product has been fully evaluated and there is no change to the Critical Quality Attributes or composition of the finished product'.<br><br>We propose removing the first part of the sentence given the lack of clarity over "fully evaluated" and because as the applicant has to confirm there are no changes to finished product release and end of shelf life, and | There is no change to the Critical Quality Attributes or composition of the finished product'. |

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| | | | there is no change to composition of finished product.<br><br>(this condition is for a new or updated certificate of suitability) | |
| 4 | 934<br><br>B.III.1.b | EFPIA/VE | The wording in B.III.1.a has been revised to remove mention of new and already approved manufacturers, which is much clearer.<br><br>A similar revision can be applied to B.III.1.b. | 1. New TSE certificate or an active substance<br>2. New TSE certificate for a starting material/reagent/ intermediate/or excipient<br>3. Update of an approved-TSE certificate<br>5. New/updated certificate using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required |
| 5 | 934<br>B.III.1<br>Documentation 2 | EFPIA/VE | Amendment of the relevant section(s) of the dossier should include:<br>-Updated consolidated list of manufacturers of the active substance (section 3.2.S.2.1).<br><br>Please confirm that the requested section 3.2.S.2.1 is a single compiled 3.2.S.2.1 MAH section including all manufacturers of active substance used by the MAH/Finished Product manufacturer. | Suggestion to include confirmation:<br>- Updated consolidated list of manufacturers of the active substance (section 3.2.S.2.1), single compiled MAH section 3.2.S.2.1 including all manufacturers of active substance used by the MAH/Finished Product manufacturer. |
| 6 | 934<br>B.III.1<br>Documentation 2 | EFPIA/VE | (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 | "In the case of an active substance, this should include: …" |

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| | | | material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient)<br><br>Documentation 2: As this category may also be used for excipients and starting materials, not all the proposed updates to the dossier will be applicable in every case | |
| 7 | 934<br>B.III.1<br>Note | EFPIA/VE | In the note highlighting cases when a separate variation may be required, reference should be made to B.I.a, but also B.I.b and B.I.d depending on the case. | Note:<br>For active substances supported by a certificate of suitability (CEP), a separate variation is required [Delete: under category B.I.a.1 scope] in the following scenarios:<br>- to register or amend sites (e.g. micronisation or control/testing sites) if these sites are not included on the CEP (under category B.I.a.1).<br>- to register or amend in-house analytical test procedures used by FPM if these analytical procedures are not included on the CEP (under category B.I.b).<br>- to register or amend a re-test period if the re-test period is not included on the CEP (under category B.I.d). |
| 8 | 935<br>B.III.2 | EFPIA/VE | Proposal is to add the word “reagents” to the change description for B.III.2 (and other relevant parts of the section) for clarity. | Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State for active substances, reagents, intermediates, excipients, immediate packaging materials and active substance starting materials. |

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| | | | | (also in all relevant subsections of this category) |
| 9 | 935<br>B.III.2.a2 | EFPIA/VE | Consider including diluents.<br><br>Rationale: diluents (for example WFI) are simple drug products and may be reported under lower reporting categories using a risk-based approach.<br><br>The term primary packaging material is more commonly used than 'immediate packaging material'. | Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State for active substances, intermediates, excipients, immediate packaging materials and active substance starting materials<br>a) 2. Proposal to include diluents |
| 10 | 935<br>B.III.2.a.2 | EFPIA/VE | The term primary packaging material is more commonly used than 'immediate packaging material'. | Proposed change to the description of the change:<br><br>"Excipient/active substance starting material/intermediate/primary packaging material" |

**B.IV Medical Devices**

| | Please insert reference to relevant scope or section *(e.g. B.IV.1, Conditions, Documentation)* | Stakeholder name *(to be repeated in all rows)* | Comment and rationale | Proposed guidance text |
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| 1 | B.IV MEDICAL DEVICES | EFPIA/VE | Please ensure consistent use of terminology as the term "medicinal product", "final product", and "finished product" are used when assessing impact of a change. | Replace definition of term "medicinal product", "final product", and "finished product"<br><br>and use only "medicinal product" when describing impact assessment on either the co-packaged medical device, referenced medical |

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| | | | Recommendation to use term “medicinal product” when assessing impact of a change - as the impact on the entire product (integral device, primary packaging and drug product, secondary packaging including co-packaged medical device) should be evaluated. | devices (including integral device (part)), as it is meaning the presentation (in whatever configuration) that is being placed on the market. |
| 2 | B.IV.1 | EFPIA/VE | Ensure consistent use of terminology and in this context, we are talking about a medical device that meets the definition per the Regulation (EU) 2017/745.<br><br>“Changes to device (parts) co-packaged with the medicinal product or referenced in the product information”.<br><br>It is important to be clear this is the Medical Device and not an integral device component, which are not covered herein this section. | Reword to state:<br><br>Changes to medical device [Delete: (parts)] co-packaged with the medicinal product or referenced in the product information<br><br>Furthermore, use ‘medical device’ rather than just ‘device’ where stated throughout. Applies also for b, c, d etc. |
| 3 | 937<br>B.IV.1 ,b | EFPIA/VE | There is no acknowledgement of possible connection to digital medical devices through the ‘referenced’ type. Even if the use of a digital app is ‘optional’ for the user, we understand through prior dialogue with EMA it should be added to the PI and subsequently the variation required to demonstrate safe and effective delivery or use with the medicinal product. | A note should be added to the table, either as part of b) requirement or separate table footnote stating:<br><br>“this includes any optional use of a digital medical device, and the applicant is required to add a statement regarding the ‘optional’ medical device in the medicinal product PI. |
| 4 | 937<br>B.IV.1.b | EFPIA/VE | Proposed to consider usability throughout the document, especially where the minor changes are referenced; to include the examples of significant impact changes. | Revise to state:<br>“Addition, replacement, or other changes to a co-packaged or referenced device that may have a significant impact on the delivery, |

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| | | | | quality, safety, efficacy of the medicinal product, and/or the usability of the device. |
| 5 | 937<br>B.IV.1.d | EFPIA/VE | For a medical device that is co-packaged (and therefore has its own, separate medical device registration) detailed, technical drawings of the device should not be required. Revision to address level of detail important for quality assessment. | Revise point 1 from Documentation list to read:<br>1. Amendment of the relevant section(s) of the dossier, including description, [Delete: detailed] drawing and composition of the device material, compatibility and usability studies as appropriate. |
| 6 | 937<br>B.IV.1.a<br>Documentation 2 | EFPIA/VE | For the documentation requirements we suggest simplification to ensure alignment with the MDR. The proof of compliance for co-packaged and referenced devices is the Declaration of Conformity or EU CE certificate. | 2. EU Declaration of Conformity, or, where applicable, EU CE certificate. |
| 7 | 937<br>B.IV.1<br>Conditions | EFPIA/VE | Conditions and documentation required for $IA_{IN}$ and IA types:<br>Condition 1 and condition 4 both address the safe delivery of the medicinal product, as no significant impact on delivery is regarded to be included in the wording of safe and accurate delivery. Therefore, to avoid redundant conditions, please consider if a merge of these conditions in one condition is possible. | It is recommended to delete condition 4, and to update the wording for condition 1 to allow a consolidated wording of 1 and 4 – proposed re-wording for Condition 1: "The device does not have a significant impact on the safe and accurate delivery or intended use of the medicinal product." |
| 8 | 938<br>B.IV.2 | EFPIA/VE | Propose revision to "integral medical device (part)" throughout B.IV.2 to be aligned with the terminology used in EMA Questions & Answers for applicants, marketing authorisation holders of | Recommend to align the terminology better with the proposed definition in the draft GPL for consistency, therefore use the following |

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| | | | medicinal products and notified bodies with respect to the implementation of the Regulations on medical devices and in vitro diagnostic medical devices (Regulations (EU) 2017/745 and (EU) 2017/746). | term within this section, and will avoid the ambiguous use of 'part':<br><br>Revise the header to read:<br>B.IV.2 Changes to an integral [Delete: combination of a medicinal product with a medical] device (part)'<br><br>Simplified as: B.IV.2 Changes to an integral device (part).<br><br>This also requires revision & alignment throughout the table |
| 9 | 938<br>B.IV.2.b | EFPIA/VE | b) Do not view a change without significant impact should be Type IB variation, if it doesn't have a big impact as it is said already in the condition.<br>Is it necessary to have a separate category b) at all? | Revise Procedure Type: IA *or* $IA_{IN}$<br><br>OR alternatively delete b) |
| 10 | 938<br>B.IV.2, b &<br>Documentation 2 | EFPIA/VE | Documentation to be provided requires an EU Declaration of Conformity (Class I device only) but legally this evidence doesn't exist. An integral medical device (part) cannot legally hold a CE mark, as it doesn't meet the definition of a medical device. Furthermore, a DoC (for Class I medical device) would be against EU MDR in full and cannot solely be for Annex I (which is only requirement of device-part of integral product). | Difficult to put forward a proposal given the existing legal framework for DOC and limitation for Class I device (part) when integral within product.<br><br>Recommendation:<br>Replace "EU Declaration of Conformity" by "Declaration of compliance with the applicable GSPRs (for Class I devices only)" as this is what |

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| | | | Per EMA Q&A Class I device part is not in scope of NB assessment. Therefore, it is unclear how legally this requirement can be fulfilled given the existing framework. | is required by Art 117 of the EU MDR (but this is not a DOC per Legislation as that is against full MDR compliance) |
| 11 | 938<br>B.IV.2.b<br>Documentation 2 | EFPIA/VE | DoC/Notified Body Opinion should not be required if the addition or replacement of an integral device (part) which does not have significant impact on Performance, delivery, quality, safety of efficacy of the medicinal product.<br>The recent V.4 of the EMA Q&A guidance indicates for non-significant changes, only a justification is required based on risk assessment of the change. | Revise point 1 from Documentation list to align and recognise the justification required in 3.2.R.2 per EMA/37991/2019 to support minor changes and would read:<br>1. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate and a justification in 3.2.R.2. summarising the risk assessment performed which concluded that the change is non-significant and there are no other changes to the integral device (part) beyond the change in question, therefore justify the absence of any revised evidence e.g. NB opinion / EU certificate/ EU declaration of conformity. |
| 12 | 938<br>B.IV.2.d<br>Changes to an integral medical device (part) | EFPIA/VE | Changes in material between d) and a) is not clear. A change in material of a device that is not in contact with the DP may still have (or not have) a significant impact on the delivery. i.e. switching from a pen fossile polymer to biomass polymer may fragilize the finished product rendering the administration more complex. | B.IV.2.d) should be reworded: "Change of a material of an integral device (part) not in contact with the medicinal product, that does not have a significant impact on the safety, quality or efficacy of the medicinal product." |
| 13 | 938 | EFPIA/VE | B.IV.2.e) The variation classification as referenced in the EMA Q&A does not match to the one proposed in the Variation Guidelines; the new | Adapt the Variations Guideline and switch B.IV.1 and B.IV.2, and cover integral medical devices in B.IV.1, while covering co- |

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| | B.IV.2.e | | applicable classification (as currently proposed) will be B.IV.2 e).<br><br>EMA/37991/2019 (Rev.4), Q&A 2.7 states for the bullet point “Change in qualitative and/or quantitative composition of a device (part)” the following “The replacement of a material (change in qualitative or quantitative composition) by an equivalent one for a medical device (part) in contact with the medicinal product should be submitted under B.IV.1 classification.” | packaged/referenced medical devices in B.IV.2 – by this, the reference given in EMA/37991/2019 (Rev.4) remains valid. |
| 14 | 938<br>B.IV.2<br>Documentation 3 | EFPIA/VE | For provision related to documentation item 3, it is unclear why 2 batches are required when minor changes only require 1 batch.<br><br>It is suggested to realign to be comparable to a minor change, as per the type IB suggests. | 3. The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least [Delete: two] one pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). |
| 15 | 939<br>B.IV.3.b and c | EFPIA/VE | Unclear which device parameters are covered by this category, if it is not part of the final specification – other specifications would not be part of a commitment section.<br><br>Please clarify that this category only covers parameters included in 3.2.P.5.1. Specification(s). | It should mention that only parameters included in 3.2.P.5.1. Specification(s) section are covered. |

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| | | | Please clarify that this category covers drug-independent device parameters only.<br><br>Please clarify that drug-dependent parameters are covered by B.II category. | |
| 16 | 939<br><br>B.IV.3 | EFPIA/VE | B.IV.3 as B.IV.2 cover changes to medical devices in integral medicinal product setups; it is not clear why there is further sub-section needed instead of ensuring coverage of all possible changes in section B.IV.2.<br><br>In addition, B.IV.2 already discusses changes to design and performance characteristics (B.IV.2.a)) as well as other minor changes (B.IV.2.h)). However, B.IV. 3 addresses the same topics:<br><br>- B.IV.3 a) covers minor changes to the dimensions (i.e. to the design of the device).<br><br>- B.IV.3b) covers changes to specifications – specifications are part of performance characteristics. | Reconsider the grouping of changes in terms of having only one section for medical devices of integral medicinal products as well as potential re-wording of changes stated to ensure that there is no redundant and/or inconsistent information given. |
| 17 | 939<br><br>B.IV.3.b | EFPIA/VE | b,1) – Does condition 4 need to apply? A specification of the device (not in final product specification may have nothing to do with the device's delivery of a medicinal product or the safety of the device. An example is perhaps flash Is allowed to be larger to a non-functional surface. It wouldn't impact delivery or safety of the device. | Delete condition 4. |

**B.V Changes to a marketing authorisation resulting from other regulatory procedures**

| | Please insert reference to relevant scope or section *(e.g. B.V.a.1, Conditions, Documentation)* | Stakeholder name (to be repeated in all rows) | Comment and rationale | Proposed guidance text |
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| 1 | 943<br>B.V.a.1<br>Documentation | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or "confirmation" in the submission should be appropriate.<br><br>Documentation 1: replace declaration by confirmation "Declaration that the PMF Certificate and Evaluation Report are fully applicable for the authorised product, PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder), the PMF Certificate and Evaluation Report replace the previous PMF documentation for this Marketing Authorisation." | Documentation 1: "[Replace: Declaration] Confirmation that the PMF Certificate and Evaluation Report are fully applicable for the authorised product, PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder), the PMF Certificate and Evaluation Report replace the previous PMF documentation for this Marketing Authorisation." |
| 2 | 944<br>B.V.a.2<br>Documentation | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and | Documentation 1: [Replace: Declaration] Confirmation that the VAMF Certificate and Evaluation Report are fully applicable for the |

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| | | | proliferation. A statement or “confirmation” in the submission should be appropriate.<br><br>Documentation 1: replace declaration by confirmation “Declaration that the VAMF Certificate and Evaluation Report are fully applicable for the authorised product, VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the Official Journal of the European Union EMA/275213/2024 Page 73/82 MAH (where the MAH is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorisation.” | authorised product, VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the Official Journal of the European Union EMA/275213/2024 Page 73/82 MAH (where the MAH is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorisation. |

**C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES**

**C.I Human medicinal products**

| | Please insert reference to relevant scope or section *(e.g. C.1.a, Conditions, Documentation)* | Stakeholder name (to be repeated in all rows) | Comment and rationale | Proposed guidance text |
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| 1 | 948-951 | EFPIA/VE | A general note is included in this section (and in lines 805-808) that an additional quality | In case of a change in therapeutic indication, posology or maximum daily dose, a review of quality documentation may be performed (e.g. the need to change impurity limits or warnings |

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| | | | review is required for changes in therapeutic indication.<br><br>It is possible that a change affecting the therapeutic indication (or posology/maximum daily dose) may not trigger any change affecting the quality of the product.<br><br>As currently worded it is also not clear what justification would be needed e.g. if the expectation is a statement signed by quality confirming that the proposed changes have no impact then this could also be part of the update/addendum to the clinical overview. It would be helpful to further clarify and include this as a document requirement C.6 Change(s) to therapeutic indication(s) | for excipients with known effect/ threshold). If the change has an impact on the quality documentation the holder must submit the corresponding updated sections of the dossier as requested in the Annex for the given change. |
| 2 | 952 C.1. and 958 C.7 | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology “declaration” could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or “confirmation” in the submission should be appropriate. | Applies to Documentation 2 in 952:<br><br>Confirmation that the proposed Summary of Product Characteristics, Labelling and Package Leaflet is identical for the concerned sections to that annexed to the Commission Decision or to the agreement reached by the CMDh (as applicable).<br><br>Applies to Documentation 1 in 958:<br><br>Confirmation that the remaining product presentation(s) are adequate for the dosing instructions and treatment duration as |

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| | | | | mentioned in the summary of product characteristics. |
| 3 | 953 C.2. | EFPIA/VE | Regarding the title of category C.2. (“Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product from the original application”). We believe that it is unclear as to what is meant by the term “original application” and propose that this is deleted.<br><br>Furthermore, Type IB should also be applicable in cases where one of the substances of a fixed dose combination is a generic and the MAH implements a change derived from that generic substance in line with the originator. | Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of generic/hybrid/biosimilar medicinal products (including when used as a fixed dose combination) following assessment of the same change for the reference product. |
| 4 | 953 C.2 | EFPIA/VE | The requirements for documentation (3.) need to be changed to allow for justification when additional clinical/safety data would not be required. | For the biosimilar medicinal product aligning the product information with an indication of the reference medicinal product: a justification that the comparability exercise performed for the biosimilar medicinal product is valid for the applied indication and that no additional clinical or safety data is needed. |
| 5 | 955 C.4 | EFPIA/VE | Category C.4 as written allows only for classification of labelling changes as a Type II variation. This means even a less significant change (e.g., adjustment to the wording of an adverse event, implementation of text already approved for a mono-component in a | No specific wording is proposed at this stage but recommend creating subcategories for changes to the SmPC, labelling or PL as follows, with variation type (IB or II) determined based on risk and the level of assessment required:<br>- Urgent safety changes |

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| | | | combination product, etc.) is classified in the same way as the addition of a new indication (C.6, also Type II) or other major change which requires assessment of substantial amounts of new clinical data and a full risk-benefit evaluation. | - Minor changes<br>- Major changes |
| 6 | 957 C.6. | EFPIA/VE | Regarding C.6.a (Addition of a new therapeutic indication of modification of an approved one), amended dossier sections might not always be required, especially in case of an amendment to an existing indication. Propose to amend the documentation listed under point (1.) | 1. Amendment of the relevant section(s) of the dossier (where applicable), including revised product information |
| 7 | 959 C. 8.a | EFPIA/VE | Within the text under 'Note:' we propose to add "on a country level" to make it clearer that this change has to be submitted nationally (it is a purely national regulatory activity/national variation) and is not subject of an EU variation if MRP/DCP products are impacted. Furthermore, it is also proposed to add "after an MA transfer" to make it clear that it is about a new legal entity and not a name change of MAH without a change in legal entity. | Note: This variation is only applicable on a country level for nationally authorized products after an MA transfer in order to prove for the new MAH that he has at his disposal …" |
| 8 | 960 C.9. | EFPIA/VE | Under point C (9b): We do not believe that updates to templates should result in a type IB variation and would propose to remove this reference. | Implementation of changes which require additional minor assessment, e.g. change to the due date of obligations and conditions of a marketing authorisation and required pharmacovigilance activities in the risk management plan, including changes to the due date of study milestones. |
| 9 | 960 C.9. | EFPIA/VE | Under condition C (1.) "The variation implements the action requested, including the | "The variation implements the action requested, including the exact agreed wording and the |

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| | | | exact agreed wording and the agreed national translations”<br><br>There might be cases where no translations are necessary e.g. for changes in the obligations for non-CAP products. Please add “if applicable” | agreed national translations, if applicable, and it does …” |
| 10 | 964 New C.13 | EFPIA/VE | We propose a new classification, to establish a mechanism for low administrative burden submission of minor changes to product information for which Article 61(3) is not applicable.<br><br>Such classification would be helpful for correction of local translation errors that do not require further assessment, or for minor changes to the common version of the product information, particularly for products with no other ongoing or planned labelling activity in which such changes could be included.<br><br>We believe that such minor changes to the common language version could currently be as Type IB by default (C.I.z) IB unforeseen. Adding a new classification would provide greater clarity. | Other minor change(s) to the Summary of Product Characteristics, Labelling or Package Leaflet<br><br>a) Update affecting the common (e.g. English) version of the product information<br>- Cond. to be fulfilled: 1<br>- Docum. To be supplied: 1, 2<br>- Proced. Type: IB<br><br>b) Update to translation(s) of the Product Information<br>- Cond. to be fulfilled: 1, 2<br>- Docum. to be supplied: 1<br>- Procedure Type: IAIN<br><br>Conditions:<br>1. The variation is not due to new quality, preclinical, clinical or pharmacovigilance data.<br>2. The common version (e.g. English for a centrally approved product) is not affected. The translations are being updated to align with the approved common version (may or may not affect all of the translations).<br><br>Documentation: |

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| | | | | 1. Revised product information in tracked and clean.<br>2. Rationale for the change |

**D. PMF/VAMF**

| | Please insert reference to relevant scope or section *(e.g. D.1.a, Conditions, Documentation)* | Stakeholder name (to be repeated in all rows) | Comment and rationale | Proposed guidance text |
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| 1 | 970<br>D.5<br>Documentation | EFPIA/VE | Considering potential adoption of EU guidelines by 3rd countries (specifically in the context of reliance): The terminology "declaration" could be perceived as a separate document therefore increasing documentation burden and proliferation. A statement or "confirmation" in the submission should be appropriate.<br><br>Documentation 2: replace "declaration" by "confirmation". | Documentation 2: [Delete: Declaration] Confirmation no changes have been implemented. |
| 2 | General comment | | Section D of the variation guidance focuses on variations specifically impacting PMFs and VAMFs. It is noted that this format is in line with how PMF and VAMF are presented in current Annex I of Directive 2001/83. Considering the need to update Annex I (i.e. future Directive Annex II) as part of the revision of the General Pharmaceutical Legislation, step 2 of the revision of the variations framework /classification guideline (after finalisation of the GPL) should also | N/A |

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| | | | consider reflecting changes to new types of master files, as appropriate, in this section D, e.g. changes to Quality Master Files or Platform Technology Master Files. | |

**Other comments**

| | Please insert reference to relevant scope or section | Stakeholder name (to be repeated in all rows) | Comment and rationale | Proposed guidance text |
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| 1 | General comment | EFPIA/VE | For analytical procedure changes throughout the annex, condition refers to validation showing the updated analytical procedure is at least equivalent to the former analytical procedure. The term “equivalent” should be replaced by the ICH Q14 terminology, see chapter “7 Lifecycle management and post-approval changes of analytical procedures” Table 2. | “The analytical procedure change evaluation should demonstrate that Analytical procedure attributes impacted by the change are evaluated, and criteria are met after change. And, as appropriate, results are comparable after change or differences are acceptable and potential impact on specification evaluated “ |
| 2 | General comment | EFPIA/VE | Currently the applicants need to consult several documents to make sure they have all the correct information. All these Q&As are not all in the same place, which makes it very time consuming and challenging to navigate through the different guidance and Q&As leading to validation questions and more time spent by both applicants/regulators at the validation stage or during evaluation process.<br><br>It is suggested to add a section for references where all documents providing further details and recommendations on | Add after line 984 a new section:<br><br>section V References:<br><br>list all relevant source of information for variation requirements and technical details (Q&A, location of technical details …) |

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| | | | variation technical information are listed as well as location where specific information may be available. | |
| 3 | General comment | EFPIA/VE | EFPIA/VE recognizes that significant steps have been made towards a simplified and effective management of changes, but in line with ICH guidance we see that there is further opportunity to utilize a science and risk-based approach. For example, rather than differentiating between small and large molecules this should be based on science and risk-based approach, there are many examples of complex small molecules and conversely there are well defined biologicals where the variations could be treated in line with a small molecule. | Broaden science and risk based classification consistently throughout the document. For example, align large and small molecule classifications and requirements based on risk assessments and prior knowledge. |
| 4 | Introduction section | EFPIA/VE | It is specified that the classification guideline will be regularly updated particularly in frame of article 5 experience. However, it is unclear if the scope of these regular updates is limited to art 5 or can be broader.<br><br>In the latter case, please clarify if an opportunity for consultation / comment prior implementation will be possible.<br><br>This would allow for a comprehensive review and identification of all impacts, constraints, adequate understanding of the new recommendation/change and overall take into account perspectives of all stakeholders.<br><br>It is also specified that the classification guideline will be regularly updated. However, the periodicity of the updates (annual or more: the wording seems to imply that more than 1 update could occur), the timing (unclear if the update would occur at a specific timing, ie: same month each year) and the plan for transition, are not provided.<br><br>More clarity and visibility on these aspects is needed.<br>Particularly with regard to provision for a transition period and | N/A |

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| | | | updated guideline implementation as this could have a significant impact on the variation preparation and supportive data generation and lead to potential validation issues as well as additional work for both HA and applicants. | |
| 5 | Declarations | EFPIA/VE | There is an increasing reliance on declarations as required documentation. It is highly likely many other agencies will use this updated guideline as a basis for their own local legislation. This will drive an increase administrative burden on applicants due to the need to provide additional wet-ink signed/authenticated statements to other agencies. | There is an opportunity to increase the significance of Conditions. Conditions should be considered binding & applicants should be required to select all applicable conditions (regardless of change category). Confirmation conditions are met could be used in lieu of declarations & would also provide reviewers with valuable, supportive information (for IB/II changes).<br>In certain cases (e.g. B.II.g.4) it would seem more appropriate for applicants to provide a justification (within M1; M3 as relevant), rather than a declaration. |
| 6 | General comment | EFPIA/VE | Propose to include a reference for the Fast Track Procedure (CMDh/290/2013) or noting to refer to CMDh website, as well as adding a reference to EMA Guideline on Influenza vaccines – Quality module (EMA/CHMP/BWP/310834/2012)? | N/A |
| 7 | 358, 369, 371, 375, 516, 527 | EFPIA/VE | Assessment Reports are only mentioned in the context of MRP (Type II / Annual Update of Human Influenza Vaccine). What about other procedures / variation types? | Consistency required across MRP/WS/National/CP Procedures |
| 8 | 505-506 | EFPIA/VE | 2.5.1. Submission of variations applications for annual update of human influenza vaccines | 2.5.1, 2.5.2, 2.5.3, 2.5.4 also apply to Covid. The complete text needs to be updated to include Covid |

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| 9 | 566-570 | EFPIA/VE | For coronavirus vaccines or any other human vaccine that has the potential to address a public health emergency in the Union, upon agreement of the relevant authorities, addition of active substance(s) under the same marketing authorisation may be allowed, resulting potentially in the co-existence (…) | Coexistence of strength should not just be for covid/pandemic. Include all types of vaccines. |
| 10 | 494 - 499 | EFPIA/VE | Section 2.5 for Covid vaccines considers cases for strain update of both annual update and outside annual update. In order to be aligned with change description B.I.a.6 "Changes to the active substance of a vaccine against human coronavirus or other vaccine that has the potential to address a public health emergency in the Union" it would help to clarify that in both cases, the supportive data package requirements would be unchanged. | If relevant, an annual update procedure for human coronavirus vaccines will be introduced by the Agency. Such procedure shall only apply after an announcement published on the Agency's website.<br>It is possible to update human influenza and coronavirus vaccines outside the annual procedure; please contact in advance the relevant authority to discuss such application, the data package including Module 3 structure and its content and the timelines in advance. In both cases supportive data package would be identical. |
| 11 | 555 and 868 | EFPIA/VE | Section 2.6 now considers human influenza vaccine and not only coronavirus vaccines: "Annexes I and II enables the active substance(s) of authorised human influenza vaccines, coronavirus vaccines or any other human vaccine that has the potential to address a public health emergency in the Union to be updated".<br><br>For consistency, it seems that "the deletion or addition of serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for seasonal influenza vaccine that has the potential to address a public health emergency in the Union" should be added in the annex | To add 2 categories of change<br>Proposed guidance text for B.I.a.6 variation, Line 868<br>c) upon agreement of the relevant authorities, addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for seasonal influenza vaccine that has the potential to address a public health emergency in the Union: Type II |

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| | | | “B.I.a.6 Changes to the active substance of a vaccine against human coronavirus or other vaccine that has the potential to address a public health emergency in the Union”. | d) upon agreement of the relevant authorities, deletion of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for seasonal influenza vaccine that has the potential to address a public health emergency in the Union: Type IB |