EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 August 2014
EMA/CHMP/CVMP/QWP/774027/2013 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)/ Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on stability testing for applications for variations to a marketing authorisation' (EMA/CHMP/CVMP/QWP/441071/2011)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	The Association of the European Self-Medication Industry (AESGP)
2	Active Pharmaceutical Ingredients Committee (APIC) / European Chemical Industry Council (Cefic)
3	European Federation of Pharmaceutical Industries and Associations (EFPIA)
4	European Generic medicines Association (EGA)
5	Hikma Farmacêutica (Portugal) S.A.
6	International Federation for Animal Health Europe (IFAH-Europe)
7	PHARMIG - Association of the Austrian Pharmaceutical Industry
8	PolyPeptide Laboratories (Sweden) AB
9	SciencePharma
10	Takeda Ireland Ltd
11	European Group for Generic Veterinary Products (EGGVP)

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

No.	Stakeholder no.	General comment (if any)	Outcome (if applicable)
1.	1 (AESPG)	Compared to the Commission guideline on the details of the various categories of variations of the terms of marketing authorisations for medicinal products for human use, this draft guideline covers additional variations and some degree of flexibility for the MAH to define what is acceptable with respect to stability information needed has been introduced. However the requirements outlined in this draft guideline are much more demanding in terms of duration of the stability studies; particularly it creates more constraints to the companies with regard to timing of submission (see comparative table below). We would apply for a more pragmatic approach consistent with the requirements laid out in the EC guideline.	Noted
2.	1 (AESPG)	We noted that "herbal drugs, herbal drugs preparations and related herbal medicinal products" are now mentioned in the scope of this draft guideline. This is not the case in the present guideline (CPMP/QWP/576/96 rev. 1). Given the complex nature of the herbal substances and preparations, which indeed contain numerous components, specific stability requirements apply to herbal substances, preparations and related medicinal products. There are a number of guidelines that have been specifically developed for herbals and reflect their specificities such as the guideline on quality of herbal medicinal products (EMA/CPMP/QWP/2819/00 Rev.2; EMA/HMPC/201116/2005 rev.), the guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products / traditional herbal medicinal products (EMA/CPMP/ QWP/2820/00 Rev. 2; EMA/CVMP/815/ 00 R ev. 2; EMA/HMPC/162241/2005 Rev. 2) and the guideline on quality of combination herbal medicinal products/traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/2006). We wonder why the same principles were not adopted here as beside the mention of 'herbals' in the scope of the guideline, there is no other mention in the body of the document, nor any reflection of their specificities with regard to stability requirements. If it remains as such this would be highly	Partly accepted General Guidelines are added (see General requirements)

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		problematic for herbals and would introduce a number of sever inconsistencies with other EMA guidance documents on stability. It is hence crucial that the specific characteristics of herbals and the possible impact on the strategy and specifications for stability testing be duly reflected in this guideline as outlined in the Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products (EMA/HMPC/3626/2009) and the Reflection paper on Markers used for quantitative and qualitative analysis of Herbal Medicinal Products and traditional Herbal Medicinal Products (EMA/HMPC/253629/2007). We have detailed these specific adjustments needed in the corresponding sections below.	
3.	2 (APIC/Cefic)	A Glossary should be included in Guideline. APIC's many years of experience with Guidelines have proven that Glossaries are indispensable because they prevent that a wide range of different interpretations of the Guideline will be triggered. Those inevitably lead to uncertainty and numerous unnecessary disputes between authorities and industry. Some examples of terms that require clear definitions (even though definitions of some of these may have been included in Glossary's within other Guidelines): "chemical substance", "products derived from biotechnology", "biologicals", "active substances known to be stable", "active substances known to be unstable", "conventional dosage forms", "critical dosage forms" (please also note the first comment of stakeholder 4 and 11)	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines. (see also General Comment 17 from EGA and 21 from Takeda)
4.	2 (APIC/Cefic)	In the subsections of Section 6 the headings include a reference to the exact Classification Number of the implied Variation. To avoid any misunderstandings it s hould be explicitly clarified that the requirements described in that subsection only apply to that specific type of Variation and not to Variations falling under different Classification Numbers.	Accepted A Sentence in Chapter 6 added ("The following Type II variations refer to specific variations as outlined in the Guidelines mentioned above")
5.	2 (APIC/Cefic)	We ask you kindly to clarify whether the guideline is or is not applicable for biologicals: The scope states that biologicals are out of scope while 2 of the variations that	Not accepted Biologicals are excluded in the Scope; changes mentioned by APIC/Cefic are not only related

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		are added relate to purely biological changes (change in packaging), while e.g. for the substantial change in process only the small molecules API substantial changes are listed, not the biologicals.	to purely biological products
6.	3 (EFPIA)	EFPIA welcomes the opportunity to comment on this draft guidance and considers that it would be a useful complement to the current Variation Regulation and guidance. Clarification on the required stability data for variations is welcomed, especially the Type II variations, where there is no requirements stated in the guideline 2010/C 17/01. The philosophies expressed and the guidance regarding Type I variations are considered helpful and we appreciate the inclusion of the risk-based approach outlined in Annex II for setting of shelf-life.	Noted
7.	3 (EFPIA)	A general request to standardise terminology within the guideline is made as there are a number of conflicting examples within the text. For example, an introduction which states that the following approaches "may be considered as acceptable" and requirements presented with the terminology "are recommended".	Accepted As far as possible the term "is / are recommended" will be used in the guideline; see also specific comment 23
8.	3 (EFPIA)	We request that the usual comment "that other approaches to those outlined in the guideline may be appropriate, if justified" will be included in the guideline. We propose that this should especially apply to Type II changes.	Noted Already covered; in the introduction it is stated: "It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches."
9.	3 (EFPIA)	The Quality by Design (QbD) concept, i.e., enhanced product knowledge and process understanding using science/risk-based approaches over the product lifecycle as embodied in ICH Q8, Q9, Q10, and Q11 should be specifically mentioned here as examples of scientifically justified alternatives to the traditional approach that relies primarily on empirical data, particularly those from formal stability studies. For example, a product developed using the QbD approach may not require formal stability studies to support a change that is well understood with regards to its impact on the quality, stability,	Partly Accepted "e.g., Quality by Design concept" is included in introduction There are specific variations added in the revised classification GL (e.g., variations B.I.e, B.II.g)

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		safety, and efficacy of the product. Within a QbD approach, the number of batches, the scale, the duration of testing and test conditions should be defined by the applicant on a risk-based approach considering the level of product knowledge and the complexity of the product. T he same consideration may also be appropriate for products developed with other approaches where extensive product and stability knowledge are available.	
10.	3 (EFPIA)	The guideline emphasizes that the applicant should assess the impact of the variation on the quality characteristics of active substances and/or drug products and "consequently on their stability." However, it does not describe what would be accepted as a w ay to assess the impact of the change on stability-related quality attributes before determining if there is a need to place a post-change batch on formal stability study. It should be specifically stated that the assessment as t o whether a change will have an impact on stability does not have to rely on formal stability studies, if science/risk-based approach is taken and enhanced product knowledge and process understanding is demonstrated.	Not accepted No need to add such a statement in case of science/risk-based approach / product knowledge and process understanding as this is covered in specific variations in the revised variations classification GL
11.	3 (EFPIA)	Overall, the proposed guidance does not differentiate enough between stable/unstable products or conventional/critical dosage forms when defining specific stability requirements. We would expect that a justification of reduced stability requirements could be made based on the inherent stability of the active substance or drug product.	Not accepted The guideline sufficiently differentiates between stable/unstable products or conventional/critical dosage forms
12.	3 (EFPIA)	There appears to b e an automatic expectation that 6 months data are required to support type II changes. This appears to be an increase from that previously expected. We suggest that 6 m onths' data may not always be necessary (see earlier comments on QbD approach). In particular, where the nature of the change does not demonstrate a clear risk to stability, and/or where the emerging data show no deterioration in profile	Not accepted For the QbD approach specific variations are listed in the variation classification GL
13.	3 (EFPIA)	It is suggested that, where formal stability studies are needed after the initial assessment, different types of data packages may be a ppropriate. F or	Not accepted Different data packages are already proposed

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		example comparative 3 months/1 batch of accelerated and long-term data for verifying an approved retest period/shelf life, while for re-establishing the retest period/shelf life, comparative 6 months/2-3 batches of accelerated and long-term data may be appropriate. The assessment should be limited to those parameters likely to be affected by the changes (e.g. dissolution, impurities. assay)	in the guideline (e.g., two batches or three batches depending on the dosage form or the stability of the active substance). The proposal to test or assess only selected parameters is not supported, because the information may not be sufficient for an adequate assessment.
14.	3 (EFPIA)	The guideline appears to recommend formal stability studies on the active substance or drug product for certain variations even when the active substance is known to be stable. If the active substance is known to be stable and there is no indication that the stability is compromised, data from formal stability studies should not be needed for either the active substance or the resulting drug product. A sentence should be included under the General requirements section to acknowledge that should existing long term and/or accelerated data be available to support the change, no additional further stability data or commitments to support the change are needed at the time of submission.	Not accepted This is already explained in the introduction: "It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches"
15.	3 (EFPIA)	We recommended that the examples given relating to type II changes are carefully worded to avoid confusion. The risk-based approach of the Variations change classification generally results in any overarching change (e.g. change in specification, packaging, composition) being sub-classified into several different change scenarios with categories ranging from IA to Type II depending on risk. The Type II examples always represent the worst-case, i.e. scenarios with significantly higher risk to the quality of the product and/or with a likelihood that a significant data package will need to be assessed. The examples in this stability draft guideline are in many cases presented with a title and opening sentence which addresses the umbrella change only (e.g. change in composition) without a reminder that the requirements which follow apply only to selected sub-categories under this title. The change reference given (e.g. B.II.a.3.b.2) does provide the precise link, but we are concerned that	Accepted Headings of Type II variations will be linked more precisely to the revised variation classification GL.

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		this may not be clearly stated as a required reference for evaluation of the individual changes.	
16.	3 (EFPIA)	Are similar guidelines available for radiopharmaceuticals, biologicals and products derived from biotechnology? If not, such guidelines should be considered	Noted No such guidelines available; GL for biologicals and biotech products not within mandate of QWP
17.	4 (EGA)	The EGA welcomes the opportunity to provide comments on the EMA Draft Guideline on stability testing for applications for variations to a marketing authorisation. In order to foster common understanding, the EGA would recommend including a glossary explaining some of the new terms used and, wherever possible, the terminology should be harmonised with that already in the variation guideline. For example, it is not clear what the term "conventional dosage form" encompasses. (please also note the first comment of stakeholder 2 and 11)	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines (see also General Comment 3 from APIC/Cefic and 21 from Takeda)
18.	4 (EGA)	The EGA understands that stability data on pilot batches would be acceptable – especially for finished dosage forms – proposes to use the wording "**of at least pilot scale**" batches throughout the whole document.	Accepted
19.	6 (IFAH)	The CHMP/CVMP GL on Stability testing for applications for variations to a marketing authorisation was first developed in 2004. At the time, IFAH-Europe proposed a separate guidance be developed by CHMP and CVMP in alignment with international standards where VICH already provides specific guidance on stability data to be available at the time of submission for a new product (VICH GL3), and which is less stringent than the ICH one. Though this approach was not followed, we maintain that reduced stability data are appropriate to support variations' applications for veterinary products. As stated above, VICH provides separate guidance to specifically answer the needs of the animal health industry. Similarly, this GL should	Not accepted In principle there are no major differences between ICH and VICH stability requirements. From a scientific point of view it makes no sense to differentiate stability testing conditions between human and veterinary medicinal products.

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		propose reduced requirements for veterinary products, where batches are often produced in smaller size and less frequently than for human medicinal products.	
20.	7 (PHARMIG)	PHARMIG – the association of the Austrian pharmaceutical industry – welcomes the opportunity to provide our comments on the draft "Guideline on stability testing for applications for variations to a marketing authorisation". We welcome the effort for a revision of the guideline which has become necessary due to the publication of the "Variation Regulation" No 1234/2008 in December 2008. Generally it is seen beneficial to work with a document which provides guidance on stability testing in case of the different types of variations. Nevertheless we think that in case of the Type II variations describing changes concerning the finished pharmaceutical products (points 6.5 to 6.8 of the document) some wording in the draft guideline might be misinterpreted. It does not seem applicable to refer to quality characteristics of the active substance when dealing with a change related to the finished product. As described in chapter B.II of the "Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products" changes which affect the finished product should also be evaluated according to their effect on the quality characteristics which may impact the stability of the finished product.	Partly accepted See specific comments
21.	10 (Takeda)	Definition section required	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines

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			(see also General Comment 3 from APIC/Cefic and 17 from EGA)
22.	11 (EGGVP)	EGGVP appreciates the efforts to provide detailed examples of data to be submitted. In the same way, we believe the guideline should be more clear in detailing and exemplifying in what cases the justification for not submitting the stability data would be sufficient (*i.e*. in cases of identical specification, profiles, *etc.*)	Noted
23.	11 (EGGVP)	EGGVP also believes it would be helpful to include a glossary of terms (*i.e.* to define terms as "conventional dosage form"). In addition, we see a need for alignment and harmonization of the terminology used is aligned and harmonized with the Guideline on Variations.	Not accepted / Noted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines.
24.	11 (EGGVP)	According to our interpretation of the guideline, only stability data on pilot batches would be acceptable (especially for finished dosage forms). We would therefore recommend the use of the wording "of at least pilot scale" through whole document.	Partly accepted

2. Specific comments on text

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
25.	32-39	3 (EFPIA)	**Proposed Change:** Suggested change in headings for Section 6, in order to align with the Commission Classification guideline: 6.3. Substantial change in the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product (B.I.a.2.b) 6.4. Change in qualitative and/or quantitative composition of immediate packaging of the active substance for sterile active substances (B.I.c.1.b) 6.5. Qualitative or quantitative composition changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product. (B.II.a.3.b.2) 6.6. Change in coating weight of oral gastro-resistant, modified or prolonged release pharmaceutical dosage forms where the coating is a critical factor for the release mechanism. (B.II.a.4.b) 6.7. Change in the manufacturing process of the finished product • B.II.b.3.b, Substantial changes in the manufacturing process of the finished product that may have a significant impact on the quality, safety and efficacy of the medicinal product, • B.II.b.3.b, Introduction of a non-standard terminal sterilisation method • B.II.b.3d-e Introduction or increase in the overage that is used for the active substance 6.8 Change in the batch size (including batch size ranges) of the finished product for pharmaceutical forms manufactured by	Partly accepted Table of contents for Section 6 (Type II variations) are changed: Headings for type II variations are rephrased in line with the revised variations classification guideline

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			complex manufacturing processes, (not applicable to standard immediate release oral pharmaceutical forms or non-sterile liquid based pharmaceutical forms). 6.9 Change in immediate packaging of the finished product • (B.II.e.1a.3. change in qualitative and quantitative composition of the immediate packaging for Sterile medicinal products) • (B.II.e.1a.4.) changes to a less protective pack, where there is a reduction in shelf life or storage conditions (B.II.e.1.b. 2.) change in the type if sterile medicinal product container.	
26.	46, 48, 51, 56, 63, 69, etc	3 (EFPIA)	**Comment:** This is guidance and hence alternative approaches, if justified, are appropriate. Thus, wording such as "have to be generated," "requirement," and "required" should be softened. **Proposed change:** Replace with "recommended" or "suggested" where appropriate.	Accepted (see also General Comment 7) As far as possible the term "recommended" will be used. Rationale: A NfG is to be considered as a harmonised Community position which if is followed by relevant parties will facilitate assessment, approval and control. Alternative approaches may be taken provided that these are appropriately justified.
27.	56-61	3 (EFPIA)	**Proposed change:** include: The Quality by Design (QbD) concept, i.e., enhanced product knowledge and process understanding using science/risk-based approaches over the product lifecycle as embodied in ICH Q8, Q9, Q10, and Q11 should be specifically mentioned here as examples of scientifically justified alternatives to the traditional approach that relies primarily on empirical data, particularly those from formal stability studies. For example, a product developed using the QbD approach may	Partly accepted "(e.g., Quality by Design concept)" is included in introduction; No need to refer to the QbD concepts to a larger extent here, as these variations are often covered in specific variations in the revised variations classification GL (B.I.e, B.II.g) See also general comment 9

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			not require formal stability studies to support a change that is well understood with regards to its impact on the quality, safety, and efficacy of the product. Within a QbD approach, the number of batches, the scale, the duration of testing and test conditions should be defined by the applicant on a risk-based approach considering the level of product knowledge and the complexity of the product.	
28.	57-61	3 (EFPIA)	**Proposed change:** "The guideline provides a general indication on the requirement for stability testing, but leaves sufficient flexibility to encompass the variety of different practical situations. A science and risk based approach, relative to the change and scientific knowledge of the active substance and/or drug product should be taken into consideration. The level of stability presented in the variation file should be proportional to the nature of actual change being proposed, as well as, the given active or drug products inherent or existing stability profile. "	Not accepted The guideline sufficiently differentiates between stable/unstable products or conventional/critical dosage forms (see General Comment 11) Flexibility already covered in the introduction ("It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches")
29.	56-70	1 (AESPG)	**Comment:** Here alternative approaches are encouraged provided that they are scientifically justifiable and sufficient flexibility seems to be given. With regard to herbals, nothing further in the guideline addresses their specificities and the need to tailor the general requirements applicable to chemically pure compounds. The introductory statement also contradicts that made under "5. Type I variations" concerning the 'minimum set of data'. As there are some special requirements for the stability concept	Already covered in lines 56 – 61 (e.g., "It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches") Partly accepted (see General requirements)

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			for herbal medicinal products it is again very important to reflect the specific characteristics of herbal drugs, herbal preparations and related herbal medicinal products in the present guideline to foster harmonisation in the EU. **Proposed change:** We would apply for the addition of the following sentence at the end of the paragraph: "…taking in particular into account the specificities of herbals".	
30.	64	2 (APIC/Cefic)	**Comment:** The term "chemical active substance" should be defined in a Glossary. The question arises whether also semi-synthetic active substances and substances that are products of fermentation are included. This should be fully clarified. We also recommend making references to the appropriate Ph.Eur. Monographs (such as 1468) to fully clarify this. **Proposed change:** Add Glossary and references to Monographs.	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines
31.	64- 65	1 (AESPG)	**Comment:** The terminology used here 'herbal *drugs*, herbal *drug* preparations and related herbal medicinal products' is not consistent with that used in Directive 2004/24/EC. **Proposed change:** Herbal substances, herbal preparations and related herbal medicines products.	Accepted
32.	66	2 (APIC/Cefic)	**Comment:** The terms "biologicals" and "products derived from	Not accepted A glossary seems not to be necessary for this

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			biotechnology" should be defined in a Glossary. We also recommend making references to the appropriate Ph.Eur. Monographs (such as 0784) to fully clarify this. **Proposed change:** Add Glossary and references to Monographs.	guideline; terms should be defined in other relevant guidelines.
33.	72-73	3 (EFPIA)	**Comment:** Although this guideline is an extension of the CHMP and CVMP guidelines on Stability Testing of Existing Active Substances and Related Finished Products and the respective ICH/VIVH Guideline for New Active Substance and Drug Products, there are several instances where the stability data recommended in this guideline may contradict those outlined in earlier guidance. **Proposed change:** Add a statement at the end to read, "The recommendation on stability data in this guideline should supersede those in other guidelines published earlier if inconsistencies are found between them."	Not accepted Discussion of possible inconsistencies should be avoided during the assessment of variations. Reference to lines 72-73 (legal basis) made by EFPIA unclear
34.	75	1 (AESPG)	**Comment:** Stability studies for finished medicinal products should not require studies for active substances, if the latter are unaffected. **Proposed change:** Add "on the finished product *or the active substance"*	Accepted "or the active substance" was added
35.	75-78	1 (AESPG)	**Comment:** Please describe as well the scenario of variations which require	Partly accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			generation of stability data on the drug substance. **Proposed change:** In cases of variations which require generation of stability data on the drug substance, the stability studies required, including commitment batches, should always be continued up to the approved retest period and the authorities should be informed immediately if any problems with the stability appear during storage, ...	"/ retest period" was added See comment from EFPIA on lines 75 - 78.
36.	75-78	3 (EFPIA)	**Comment:** The draft guideline states "In cases of variations which require generation of stability data on the finished product, the stability studies […] should always be continued up to the approved shelf-life […]". Comment: Should consistently use the term drug product rather than finished product throughout. For clarity, the same requirement should also be set for the active substance, i.e., stability studies should always be continued throughout the approved retest period. **Proposed change:** In cases of variations which require generation of stability data on the drug substance, the stability studies required, including commitment batches, should always be continued up to the approved retest period and the authorities should be informed immediately if any problems with the stability appear during storage.	Partly accepted Terms drug product / drug substance are not accepted: The terms "finished product" and "active substance" are used in the European legislation and the variations classification guideline "/ retest period" was added; see comment from AESPG on lines 75 – 78
37.	77-78	1 (AESPG)	**Comment:** Due to the specific requirements of the stability testing concept	Not accepted Similar as for chemical substances

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			for herbal medicines, in some cases for stability results it is difficult to assess whether a single finding is out of specification or not. It is therefore proposed to change the term to "confirmed out of specification results". **Proposed change:** "...the authorities should be informed immediately if any problems with the stability appear during storage, e.g. if outside specification or potentially outside specification. In case of herbal preparations and related herbal medicinal products confirmed out of specification results shall be communicated."	
38.	78	1 (AESPG)	**Comment:** What is the meaning of "*potentially* outside specification"? **Proposed change:** Delete "potentially outside specification"	Not accepted Commitment Batches are on the market; if there is a trend to receive OOS results before the end of the shelf life authorities should also be informed as soon as possible; condition laid down in Classification GL Similar comments from AESPG, EFPIA and IFAH
39.	78	3 (EFPIA)	**Comment:** what is the definition of "potentially outside specification"? **Proposed change:** Define potentially outside specification or delete reference to it	Not accepted Commitment Batches are on the market; if there is a trend to receive OOS results before the end of the shelf life authorities should also be informed as soon as possible; condition laid down in Classification GL Similar comments from AESPG, EFPIA and IFAH
40.	78	6 (IFAH)	**Proposed change:** Amend to read: *"… storage, e.g. if outside specification ~~or potentially outside specification~~."*	Not accepted Commitment Batches are on the market; if there is a trend to receive OOS results before the end of the shelf life authorities should also

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
				be informed as soon as possible; condition laid down in Classification GL Similar comments from AESPG, EFPIA and IFAH
41.	79-88	3 (EFPIA)	**Comment:** This needs to consider the availability of historical and/or existing stability data and the stability profile of the active substance and drug product. **Proposed change:** "The scope and design of stability studies for variations and changes are based on the knowledge and experience acquired on the active substances and drug products. The available stability studies and or stability profiles must be taken into account.	Not accepted. No need to shorten the text in the GL
42.	83	1 (AESPG)	**Comment:** As outlined in the Guideline on stability testing of existing active substances and related finished product, (EMA/CPMP/QWP/122/02 rev 1 corr) stress tests are usually considered unnecessary for herbal drugs and herbal drug preparations. This should be reflected accordingly in this guideline. **Proposed change:** Please add "Stress tests are usually considered unnecessary for herbal drugs and herbal preparations."	Accepted
43.	83	2 (APIC/Cefic)	**Comment:** Stress testing is not always required for generic active substances.	Accepted Stress tests on active substances not necessary

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: Add "if applicable" after "stress testing"	in case of EP substances
44.	85	1 (AESPG)	**Comment:** As outlined in the Guideline on stability testing of existing active substances and related finished product, (EMA/CPMP/QWP/122/02 rev1 corr) for herbal drugs and herbal drug preparations testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C are clearly labelled on the product. This should be reflected accordingly in the present guideline. **Proposed change:** Please add "For herbal drugs, herbal drug preparations and related herbal medicinal products testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C are clearly labelled on the product. Please refer to the CHMP/QWP Guideline on stability testing of existing active substances and related finished product (EMA/CPMP/QWP/122/02 rev 1 corr)."	Partly accepted Exception only for herbal substances and herbal preparations
45.	88,107	11 (EGGVP)	**Comment:** For finished products it is justified to not perform an accelerated stability study if the Variation applied for is a like-for-like Variation. These are typically the Type IA Variations. For example, when one would change a container type for a solid pharmaceutical form and the proposed container is at least equivalent to the approved current material in respect of its relevant properties, it is clear that no differences in stability	Partly accepted In principle, the need for stability testing in accelerated testing conditions is part of the ICH/VICH stability testing package. If justified other approaches are possible (see introduction). A footnote ("according to ICH/VICH conditions, where appropriate, intermediate storage conditions, if applicable")

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			might occur over time; *i.e.* instead of a 80µm LDPE plastic bag, the applicant intends to change to a 120µm LDPE plastic bag. It is definitely not expected that any stability problems occur with the proposed 120µm LDPE plastic bag. However, to make sure that definitely no changes occur during stability, a long-term stability study is justified. The proposed additional accelerated stability study has no additional value in this case. Please refer to "Variation B.II.e.1.a.1" regarding variation of the container closure system. It would make more sense to incorporate the test for accelerated stability studies only for the Variations with a higher impact, like the relevant Type IB and the relevant Type II Variations.	is added.
46.	89	1 (AESPG)	**Comment:** The term "the applicant has to investigate whether the intended change will have an impact..." tend to suggest an assessment based on data generated for the variation. There are cases where it is justified not to generate new stability data. It is therefore proposed to change the term "investigate" to "the applicant has to assess whether the change will have an impact…". **Proposed change:** Please amend this section: "In all cases of variations, the applicant has to ~~investigate~~ **assess** whether the intended change will have an impact or not on the quality characteristics of active substances and/or finished products and consequently on their stability."	Accepted Term "assess" will be used
47.	89-91	3 (EFPIA)	**Comment:** The guideline emphasizes that the applicant should assess the	Partly accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			impact of the variation on the quality characteristics of active substances and/or drug products and "consequently on their stability." However, it does not describe what would be accepted as a way to assess the impact of the change on stability-related quality attributes before determining if there is a need to place a post-change batch on formal stability study. It should be specifically stated that the assessment as to whether a change will have an impact on stability does not have to rely on formal stability studies, if science/risk-based approach is taken and enhanced product knowledge and process understanding is demonstrated. Overall, the proposed guidance does not differentiate enough between stable/unstable products or conventional/critical dosage forms when defining specific stability requirements. We would expect that a justification of reduced stability requirements could be made based on the inherent stability of the active substance or drug product. **Proposed change:** Revise to read, "In all cases of variations, the applicant should assess whether the intended change has the potential to impact the quality characteristics of active substances and/or drug products. In some cases, this may be well understood from the development of the product based on scientific understanding and risk assessment; in other cases, formal stability studies may be necessary.	Science/risk based approach is covered in the introduction of the GL as well as in the variations classification GL The guideline sufficiently differentiates between stable/unstable products or conventional/critical dosage forms (see also general comment 11) "has to assess" instead of "has to investigate" will be used "has the potential to impact" instead of "will have an impact" will be used
48.	97-99 General Requirements	4 (EGA)	**Comment:** The EGA very much welcomes the inclusion of the reference to the Guidance on Bracketing and Matrixing Designs for Stability Studies.	Not accepted In the "General Requirements" it is clearly stated, that bracketing and matrixing concepts

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			Experience shows that the above mentioned concepts appear more readily accepted by regulatory authorities in the context of Type II variations where applicants have room for justification than for Type IA and IB variations where more prescriptive approaches are usually applied. **Proposed change:** The EGA would recommend a specific reference to the fact that the bracketing and Matrixing concepts should equally apply to all types of variations provided a rationale accompanies the stability study design.	may be applied across related products. This covers all types of variations. Because of the nature of type II variations applicability of the bracketing and matrixing concept is probably more useful in case type II variations.
49.	97-100	6 (IFAH)	**Comment:** The introduction of a reference to the concept of bracketing and matrixing is welcomed.	Noted
50.	99	1 (AESPG)	**Comment:** The guidelines reflecting specific features of herbal drugs, herbal preparations and related herbal medicinal products are not referenced here. **Proposed change:** We propose to add: "For herbal drugs, herbal preparations and related herbal medicinal products the guideline on quality of herbal medicinal products / traditional herbal medicinal products (EMA/CPMP/QWP/2819/00 Rev. 2; EMA/CVMP/814/00 Rev. 2; EMA/HMPC/201116/2005 Rev. 2), the guideline on specifications: test procedures and acceptance criteria for herbal substances , herbal preparations and herbal medicinal products / traditional herbal medicinal products (EMA/CPMP/QWP/2820/00 Rev. 2; EMA/CVMP/ 815/00 Rev. 2;	Partly accepted General Guidelines are added

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			EMA/HMPC/162241/2005 Rev. 2) and the Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/2006), the Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products (EMA/HMPC/3626/2009) and the Reflection paper on Markers used for quantitative and qualitative analysis of Herbal Medicinal Products and traditional Herbal Medicinal Products (EMA/HMPC/253629/2007) also apply."	
51.	100	3 (EFPIA)	**Comment:** Accelerated Stability Assessment Protocol is commonly used as supportive information for extrapolation of shelf-life for the finished product **Proposed change:** Data collected under accelerated conditions can be used as supportive data for extrapolation of shelf-life for the finished product. See annex 2 for further information.	Not accepted No need to revise the text; details for extrapolation are outlined in Annex II
52.	103-106	1 (AESPG)	**Comment:** As outlined in the comments on lines 56-61 the term "minimum set of data to be required" is misleading and does not reflect the introduction of the present draft guideline. The EC guideline on the classification of variations provides detailed and often tightened stability requirements compared with the previous guideline for type I variations without taking into account the special requirements for herbal drugs, herbal preparations and related herbal medicinal products. This should be clarified in the present guideline.	Not accepted IA fixed definition Other approaches are not excluded, but not IA

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: It is proposed to amend this section to "If a variation to a marketing authorisation fulfils the conditions defined in Commission Regulation EC 1234/2008 for Type IA variations, and if stability data are required, the ~~minimum~~ set of data to be submitted with the variation is defined in the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. **Alternative approaches e.g. for stability testing of herbal drugs, herbal preparations and related herbal medicinal products are possible if scientifically justified."**	
53.	106-110	3 (EFPIA)	**Comment:** The text suggests that comparative stability data would be expected as part of the variation. If this is the case, the variation guideline should be updated to note the inclusion of comparative stability data as appropriate. It would be helpful to describe "comparative stability data" as part of the General Requirements The draft guideline states: "The results of these studies […] should be compared to the results of studies performed on the unchanged active substance/drug product […]". Whereas it is clear that new stability as defined in the Variation Regulation must be submitted, it should be clarified whether the comparison with "old" data need to be actually submitted or if a summary of the findings is sufficient. **Proposed change:** "The comparison based on 3 or 6 months of accelerated data and available long-term data is intended to determine, in a qualitative manner, that no significant	Accepted Relevant sentences (comparative stability data) moved from section 5 to section 4 Rephrased to "The comparison data of the unchanged product submitted with the variation may come from earlier studies"

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			deviations from the normal stability profile (including trends and variability) have occurred in order to predict that the specification limits of the active substance/finished product will still be met at the end of the proposed retest period/shelf-life.	
54.	106-112	1 (AESPG)	**Comment:** As outlined in the Guideline on stability testing of existing active substances and related finished product, (EMA/CPMP/QWP/122/02 rev 1 corr) for herbal drugs and herbal drug preparations testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product. Consequently this applies for the finished product. This should be reflected accordingly in the present guideline. **Proposed change:** Please add "For herbal drugs, herbal preparations and related herbal medicinal products testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant. Please refer to the CHMP/QWP Guideline on stability testing of existing active substances and related finished product (EMA/CPMP/QWP/122/02 rev 1 corr)."	Not accepted Exception only for herbal substances and herbal preparations
55.	107	3 (EFPIA)	**Comment:** Recommend to state "and/or" as accelerated conditions may not always be required for the type of change e.g where long-term data are available. **Proposed change:** "using accelerated and***/or*** long-term	Partly accepted Term rephrased; accelerated testing conditions without long term testing not acceptable

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			testing conditions"	
56.	111-112	1 (AESPG)	**Comment:** The sentence "the comparison data for the unchanged product may come from earlier studies..." is part of the paragraph dealing with Type IA variations although this is valid for all types of variation. **Proposed change:** We suggest moving this sentence to make clear that this statement is valid for all variation types.	Accepted Sentence moved from section 5 to section 4 Similar to EFPIA comment on lines 111 – 112
57.	111-112	3 (EFPIA)	**Comment:** The sentence "the comparison data for the unchanged product may come from earlier studies..." is part of the paragraph dealing with Type IA variations although this is valid for all types of variation. **Proposed change:** relocation of this sentence to make clear that this sentence is valid for all types of variation	Accepted Sentence moved from section 5 to section 4 Similar to AESPG comment on lines 111 – 112
58.	126	3 (EFPIA)	**Comment:** The guidance which follows on Type II examples should be put into context. **Proposed change:** Add: The following examples outline expectations for selected Type II changes. Other approaches may be acceptable, if appropriately justified. The changes addressed under the general headings below are only those which must be submitted as Type II. Section 5 addresses requirements for IA	Partly accepted Sentence added: "The following Type II variations refer to specific variations as outlined in the Guidelines mentioned above" "other approaches" already covered in the introduction

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			and IB category changes.	
59.	126	3 (EFPIA)	**Comment:** The data to be submitted with these variations are defined in several cases in early guidelines and, in some cases, there is a discrepancy between this guideline and the earlier ones. **Proposed change:** Replace this statement with the following: "This guideline provides recommendations on (1) the assessment of the impact on stability and (2) the types and amounts of stability data, to support specific Type II variations."	Partly accepted "The following Type II variations refer to specific Type II variations as outlined in the Guidelines mentioned above. " and "The stability data outlined below should to be part of the documentation at submission of the variation" was added.
60.	126	4 (EGA)	**Comment:** In line 126 the draft text reads "However data to be submitted with these variations are not defined in the majority of cases." The EGA does not support the basic principle through which extensive stability data should be provided at the time of the variation type II submission. The EGA believes that all changes described in section 6 of the draft guideline will all entail stability study programmes through GMP requirements. Moreover, type II Variation procedures timelines are already long and imposing the provision of extensive stability data at time of submission would create massive delays in operating changes to products/processes without direct correlation to benefits for patients. A maximum of 3 month stability data along with a commitment by applicants that they will provide data as soon as the	Not accepted See also comment (59), 74, 81, 86, 96, 103, 112, 127, 145 Type II variations are major variations which may have a significant impact on the quality of a medicinal product. Necessary stability data depend on the nature of the variation; maximum of 3 months not sufficient in many cases of type II variations.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			study(ies) is(are) completed should be sufficient. Indeed, as the variation procedure is concluded, stability programme would generally be completed and data would already be available in most instances. **Proposed change:** The EGA proposes to change the draft text as follows: "However supportive stability data to be submitted with these variations are not defined in the majority of cases. Generally, at the time of submission, applicants will be required to provide a maximum of 3 month stability data along with a commitment to complete the necessary stability programmes and to provide stability study(ies) outcome in a timely manner."	
61.	127-135 Type II Variations New manufacturer of API – ASMF (B.I.a.1.b)	4 (EGA)	**Comment:** This section introduces a requirement for the provision of 6 month stability data for the introduction of a new API manufacturer supported by an ASMF, which is twice as much as required in CPMP/QWP/576/96 rev.1. Additionally, the revised draft guideline no longer makes any differentiation between unstable and stable active substances. **Proposed change:** The EGA believes the distinction between stable and unstable active substances should be re-introduced in the final guideline text and that stability studies requirements for active substances are correlated to the stability of the active substance i.e. 3 month stability requirement for stable active substances and 6 month stability data requirements for unstable active substances.	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
62.	127-135 Type II Variations New manufacturer of API – ASMF (B.I.a.1.b)	4 (EGA)	**Comment:** The guideline text is not specific enough regarding requirements to provide stability data on finished products for the introduction of a new active substance (with ASMF). The EGA supports the general basic principle through which stability data on the finished product should not be necessary in cases where the specification of the finished product is not affected by the change in active substance. On the contrary, where there are indications that the change in the active substances characteristics/impurity profiles would have an impact on the specification or on the stability of the finished product, the additional requirement for stability data on the finished product should apply. **Proposed change:** Please amend as follows: (after line 131) "In principle, stability data on the finished product will not be expected at the time of submission. However, if the quality characteristics/impurity profile of the active substances […] six months on two batches of at least pilot scale, may be required. "	Not accepted Addition not necessary
63.	127-135 Type II Variations New manufacturer of API – ASMF	4 (EGA)	**Comment:** Regarding the timing of the submission of the full stability data on the finished product (where they apply – see above comment), we would like to highlight here that as stated in EGA comment on line 126, at the time of the variation submission, 3 month stability data should suffice when accompanied by a commitment to undertake the stability programme and to provide stability study outcome when available.	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	(B.I.a.1.b)		**Proposed change:** The second paragraph should clearly reference the timing of submission of the actual data.	

64.	127-135	6 (IFAH)	***6.1. Introduction of a new manufacturer of the active substance supported by an ASMF (B.I.a.1.b)***
			
			Comment: to address the need for reduced stability studies for veterinary products', we propose the following change.
			
			Proposed change: "If the quality characteristics / impurity profile of the active substance are changed in such a way that it may impact the stability of the finished product, additional stability data on the finished product, in accelerated and long term conditions ~~six months on two batches on at least pilot scale~~, may be required, as follows:
			For (veterinary) conventional dosage forms and when the active substance is known to be stable: 3 months on 1 batch on at least pilot scale;
			For (veterinary) critical dosage forms or when the active substance is known to be unstable: 6 months on 2 batches on at least pilot scale.
			This section should also specify that if no stability data are available from the open part of the ASMF, then stability data provided by the applicant should be accepted.
				Not accepted
				Results of 3 months stability studies on 1 pilot batch are not significant even in case of conventional dosage forms (After 3 months there are only results of the initial testing and the first testing point).
				
				Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation

65.	127-218	1 (AESPG)	**Comment:** In sections 6.1 to 6.3, it is referred to "at least pilot scale batches" but thereafter in section 6.4 to 6.8 to "pilot scale batches" and then in section 6.9 to "pilot batches".	Accepted The wording "x months on at least y batches of at least pilot scale" should be used.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			We are not sure as to the reason for the change of wording and in the absence of a precise reason, we would favour consistent wording throughout the document. We assume there is the word ' scale' missing in the case of the last one (section 6.9). **Proposed change:** for consistency all described variations should use the same wording for the batch size if there is no other reason.	
66.	127/136/ 152/165/ 170/179/ 185/199/ 212	1 (AESPG)	**Comment:** We propose to mention the variation number upfront followed by its definition so as to facilitate the navigation of the document by users.	Accepted Headings in Chapter 6 changed
67.	129-131	3 (EFPIA)	**Comment:** It should be possible to establish a retest period by performing stability studies in parallel. **Proposed change:** "In case of an introduction of a new manufacturer of the active substance that is supported by ASMF stability data should be part of the applicant's part of the ASMF. In cases where no retest period is fixed (according to the relevant guidelines) the active substance has to be tested immediately prior use. A commitment to perform stability studies to establish a retest period should be made in parallel."	Not accepted Stability studies (if necessary) should be available at submission of the variation; an introduction or extension of a retest period is a separate variation (B.I.d.1.a). Grouping with a change of the retest period is possible.
68.	129-131	8 (PolyPeptide)	**Comment:** Please consider clarifying, as this section is not quite clear regarding the amount of stability data required.	Not accepted Comment unclear

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
69.	129-131	9 (Science)	**Comment:** Stability results for active substance could be performed and presented also by the drug product manufacturer. This information should be added to paragraph. **Proposed change:** In case of an introduction of a new manufacturer of the active substance that is supported by an ASMF and no retest period/shelf-life is fixed (according to the relevant guidelines) the active substance has to be tested immediately prior use. Eventually stability study could be performed and presented by the drug product manufacturer. In this case the drug product manufacturer may propose retest period for active substance.	Not accepted Change in retest period is a separate variation
70.	132-135, 143, 149, 156, 161, 162, 189, 202	3 (EFPIA)	**Comment:** The guideline emphasizes that the applicant should assess the impact of the variation on the quality characteristics of active substances and/or drug products and "consequently on their stability." However, it does not describe what would be accepted as a way to assess the impact of the change on stability-related quality attributes before determining if there is a need to place a post-change batch on formal stability study. It should be specifically stated that the assessment as to whether a change will have an impact on stability does not have to rely on formal stability studies, if science/risk-based approach (e.g. QbD) is taken and enhanced product knowledge and process understanding is demonstrated. Overall, the proposed guidance does not differentiate enough between stable/unstable products or conventional/critical dosage forms	Not accepted There are specific recommendations for QdD approaches / (e.g., Quality by Design concept)" included in introduction as well as in the Classification GL

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			when defining specific stability requirements. We would expect that a justification of reduced stability requirements could be made based on the inherent stability of the active substance or drug product. **Proposed change:** When there is no change in the characteristics and/or impurity profile of the active substance, stability on the drug product may not be required in the variation submission. If the quality characteristics/impurity profile of the active substance are changed in such a way that it will impact the stability of the finished product, additional stability data on the finished product, in accelerated and long term conditions, three or six months on two batches on at least pilot scale, may be required.	
71.	132, 143, 149, 162, 189, 202	3 (EFPIA)	**Proposed change:** If the stability-related quality attributes of the active substance are changed, a stability risk assessment on the drug product should be conducted. Where the stability-related quality attributes of the drug product are also affected, 3 months of comparative accelerated and long-term stability data on one batch of the drug product at pilot scale may be appropriate at submission, with a commitment to continue the stability study through the proposed shelf life.	Not accepted Stability data (1 batch / 3 months) not sufficient
72.	132, 143, 151, 156, 161, 189, 202	3 (EFPIA)	**Comment:** If drug substance is known to be stable then formal stability studies may not be required.	Not accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: If stability of the drug substance is demonstrated to be comparable before and after the change, no formal stability studies on the drug substance may be necessary. If stability-related quality attributes, e.g., degradation products, particle size if relevant, of the drug substance are changed, comparative stability data on the active substance are recommended in accelerated and long term testing conditions. A risk based approach, relative to the manufacturing process change proposed and scientific knowledge of the active substance should be taken into consideration. The level of stability presented in the variation file should be proportional to the nature of actual change being proposed as well as its inherent or existing stability profile.	
73.	132-135 149-151 162-164	11 (EGGVP)	**Comment:** As long as the new manufacturer of the active substance (which is supported by an ASMF) has an active substance which conforms to the pre-set requirements, of for example its corresponding Ph. Eur. Monograph, the impact for the stability of the final product is negligible, even if the impurity profile of the active substance has been changed. The impact is negligible, because the old active substance (which complied to the same requirements) has already been tested during stability studies of the final product in the past. Consequently, when the specifications for the active substance have not changed, there is no need to perform additional stability studies on the final product.	Not accepted Additional stability studies may be necessary if there may be an impact on the stability of the finished product (e.g., impurity profile, particle size, polymorphic form).
74.	134	1 (AESPG)	**Comment:** We refer to our general comments	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: Proposal for replacement: "six months stability data on two batches on at least pilot scale, may be required" to be replaced by: "**three** months stability data on two batches on at least pilot scale, may be required."	this type of variation.
75.	134, 148, 151, 161, 164, 168, 174, 177, 183, 194, 197, 207, 210, 218	3 (EFPIA)	**Comment:** 3 months stability data versus 6 months data needs to be explained and clarity given on when 6 months may be expected. **Proposed change:** Suggested wordings as below: If the quality characteristics of the active substance are changed in such a way that it may impact the stability of the finished product, additional stability data on the finished product, in accelerated and/or long term testing conditions, three months on two batches on at least pilot scale, may be required." The stability studies should be continued through the retest period/shelf life.	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.
76.	134, 151, 164	2 (APIC/Cefic)	**Comment:** In all three sections 6.1, 6.2 and 6.3 it is stated that for dosage forms 6 months testing on 3 pilot batches is required. However, according the current guidance of 2005 only 3 months on 2 batches are required. We do not see any reason to extend the time frame and number of batches. **Proposed change:** Change the requirements back to those included in the 2005 guidance: 3 months on 2 batches.	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
77.	134, 151, 164	3 (EFPIA)	**Comment:** Three months were requested in the previous guideline **Proposed change:** three months may be requested	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.
78.	136-151 Type II Variations Change in manufacturer of API SM, reagent intermediate (B.I.a.1.c)	4 (EGA)	**Comment:** The EGA believes the different stability data requirements for active substances and finished product are not justified. In addition, the current draft text introduces an extended requirement for finished product stability data (i.e. 6 months) compared to the current requirement of guideline CPMP/QWP/576/96 rev.1 (i.e. 3 months). It is important to note that these changes typically impact the restricted part of ASMFs and that ready access to this information conditions the evaluation of the potential impact of the active substance change on the finished product. **Proposed change:** The stability requirements applicable to actives substances and finished product should be aligned to reflect the potential risk of impact on the finished product. "for active substances known to be stable: three months on one batch of at least pilot scale (see Annex I for the definition of stable active substance). - for active substances known to be unstable: six months on three batches of at least pilot scale. If the quality characteristics of the active substance are	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			changed in such a way that it may impact the stability of the finished product, additional stability data on the finished product, in accelerated and long term testing conditions, three or six months on two batches (where stable and unstable active substances are involved, respectively) on at least pilot scale, may be required."	
79.	136-151	4 (EGA)	**Comment:** Please refer to EGA comment to line 126 regarding timing for submission of stability data.	Not accepted See outcome on EGA comment on line 126
80.	145	1 (AESPG)	**Comment:** For accelerated testing see comments on line 106-112 above. **Proposed change:** Please add "For herbal drugs, herbal preparations and related herbal medicinal products, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C are clearly labelled"	Accepted (see General requirements)
81.	146-148 159-161 174-177 182-183 194-197 207-210	2 (APIC/Cefic)	**Comment:** The terms "substances known to be stable" and "substances known to be unstable" should be defined in a Glossary. **Proposed change:** Add Glossary	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines (Decision at 63 QWP). Terms "substances known to be stable" is already defined in Annex I of this GL See also General comment 3
82.	146-151 159-164	11 (EGGVP)	**Comment:** EGGVP would like to stress out that is a bit strange to required 3 months stability data of one batch for stable active substance	Partly accepted The text is rephrased and reference is made for the active substance to the guideline on stability

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			and 6 months for 2 batches of the finished product. The old guide required 3 months stability data, which is more appropriate and in line with the active substance requirements. Besides, as these type of changes are a part of the restricted part, it is very important for the manufacturer of the finished product to get the 3 months stability data of the active substance to estimate the changes and the influence to the finished product.	testing of existing active substances and finished products. Minimum of 6 months stability data for the finished product at time of submission are considered to be reasonable for this type of variation.
83.	148, 161	9 (Science)	**Comment:** In some cases there is only possibility to manufacture active substance in production scale, two such batches should be enough for stability studies. **Proposed change :** - for active substances known to be unstable: six months on <u>two batches of production scale</u> or three batches of at least pilot scale.	Not accepted Data basis in case of two batches seems not to be sufficient.
84.	149-151	1 (AESPG)	**Comment:** The generation of stability data for the finished product should only be requested if high probability for impact on the stability of the related finished product is foreseen. In the current guideline, three months stability data are requested at the time of submission for all changes related to the active substance with impact on the finished product. This has now been extended to six months at the time of submission of the variation in the current draft. As in the case of variations historical data and experience with the product concerned should be available this means a further delay in submission of	

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			a type II variation, which is not seen as adequate as authorities have to be informed if problems with the stability testing appear. We therefore propose to leave the requirement of 3 months stability data for the finished product concerned at the time of submission of the variation. For accelerated testing see comments above. **Proposed change:** If the quality characteristics of the active substance are changed in such a way that it ~~may~~ ***will*** impact the stability of the finished product, additional stability data on the finished product, in accelerated and long term condition, **three months** on two batches on at least pilot scale, may be required. **For herbal drugs, herbal preparations and related herbal medicinal products, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product.**	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation. "will" instead of "may" not acceptable Not accepted Exception only for herbal substances and herbal preparations
85.	152	3 (EFPIA)	**Comment:** Insert the word 'substantial' to be consistent with the Variation Classification guideline. **Proposed change:** "6.3. Substantial change in the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product."	Accepted The title of this variation was changed in accordance with the revised variations classification guideline

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
86.	152-161	1 (AESPG)	**Comment:** In the EC guideline on the classification of variations, all changes in the manufacturing process of the active substance related to a herbal medicinal product in particular a change of geographical source, manufacturing route or production are classified as type II variations. The parallel is not true for purely chemical compounds. In the European Pharmacopeia the quality of a herbal drug is defined by the compliance with a monograph without regarding the geographical source. For herbal drugs not described in a Ph. Eur. monograph a dedicated specification taking into account the specific requirements of the herbal drug examined has to be set up in accordance with the guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products (EMA/CPMP/QWP/2820/00 Rev. 2; EMA/CVMP/815/00 Rev. 2; EMA/HMPC/162241/2005 Rev. 2) and the general requirements of the Ph. Eur. monograph Herbal Drugs. As long as the change of the geographical source has no impact on the herbal drug specification the change in geographical source only should not qualify for a type II variation requesting stability data. In the present guideline this is reflected in 6.3 *Change in the*	Partly accepted Separate heading for "Change in the manufacturing process of the active substance relating to a herbal medicinal product and there is the change to any of the following: geographical source, manufacturing route or production" in accordance with the revised classification guideline. Not accepted Classification is fixed in the Guideline

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			manufacturing process of the active substance and although variation B.I.a.2.d specifically concerns herbal drugs and herbal preparations, no specific requirements are reflected in the present draft. **Proposed change:** It is proposed to divide chapter 6.7 in B.I.a.2.b. (for chemical active substances) and B.I.a.2.d (for herbals drugs and herbal preparations). For B.I.a.2.d we propose the following wording: **"In case of variations to the manufacturing process of the active substance of a herbal medicinal product, the following approaches may be considered as acceptable:** **a/ For changes in geographical source: If the specification of the herbal drug used as starting material is not affected: comparative batch analysis data on two production batches for all specification parameters of the relevant herbal drug have to be provided. Stability testing usually may be omitted.** **b/ If the quality characteristics of the active substance change in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the active substance before and after the change. Testing at the accelerated storage condition or at the intermediate storage**	

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product. - **for active substances known to be stable: three months on one batch of at least pilot scale (see Annex 1 for the definition of stable active substance).** **for active substances known to be unstable: six months on three batches of at least pilot scale."**	
86a.	152-164 Type II Variations Change in manufacturing process of the active substance (B.I.a.2.b, B.I.a.2.d)	4 (EGA)	**Comment:** Please see previous EGA comment to line 136-151 above. **Proposed change:** Please align active substance and finished product stability data requirements (see proposed change under EGA comment to line 136-151 above)	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.
87.	152-164	4 (EGA)	**Comment:** Please refer to EGA comment to line 126 regarding timing for submission of stability data.	Not accepted See outcome on EGA comment on line 126
88.	162 - 164	1 (AESPG)	**Comment:** In the current guideline three months stability data were requested at the time of submission for all changes related to the active substance with impact on the finished product. This	Not accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			has been extended to six months now in the draft guideline. As in the case of variations, historical data and experience with the product concerned should be available, this means a further delay in submission of a type II variation. This does not seem appropriate given that authorities have to be informed if problems with the stability testing appear. We therefore propose to leave the requirement of 3 months stability data for the finished product concerned at the time of submission of the variation. The generation of stability data on the related herbal medicinal product should be requested only if there is a high probability for impact on the stability of the related herbal medicinal product. Otherwise significant costs without added value are generated. For accelerated testing see comments in previous sections. **Proposed change:** If the quality characteristics of the active substance are changed in such a way that it ~~may~~ **will** impact the stability of the *related herbal medicinal product*, additional stability data on the finished product, in accelerated and long term condition, **three** ~~*six*~~ months on two batches on at least pilot scale, may be required. **For herbal drugs, herbal preparations and related herbal medicinal products, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product.**	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation. "will" instead of "may" not acceptable Partly accepted (see General requirements) Exception only for herbal substances and herbal preparations

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
89.	165	3 (EFPIA)	**Comment:** Rewording required ensuring alignment with the Variation Classification guideline. **Proposed change:** 6.4. Change in qualitative and/or quantitative composition of immediate packaging of the active substance for sterile active substances (B.I.c.1.b)	Accepted The title of this variation will be changed in accordance with the revised variations classification guideline
90.	165-168	3 (EFPIA)	**Comment:** Whilst we understand why a primary packaging change for a sterile active substance is classified as Type II (microbiological integrity), we do not comprehend why more *stability* data are needed in support of the change just because the active substance is sterile. The same molecule, non-sterile, would classify as Type IA and would need maximally 3 months' data to be available at submission; if the new packaging were more protective, submission can even be made before the data are available. **Proposed change:** Change six to three and add that with a more protective packaging, the data need not be available at time of submission.	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation (sterile active substances). Non–sterile active substances = IA (3 months / 2 batches) Liquid non sterile active substances = IB (3 months / 2 batches)
91.	165-169 Type II Variations Change in immediat e	4 (EGA)	**Comment:** The stability of the active substance and its sterility have no direct correlation. According to the variation guideline, the suitability of the packaging material should be confirmed by 3 month stability data results on at least two pilot scale batch.	Not accepted. This type II variation (B.I.c.1.b) only covers sterile active substances (and non-frozen biological/immunological active substances

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	packaging of the active substance (B.I.c.1.b)		The same approach should be applicable for sterile products, even if the type of the change is different. **Proposed change:** Please amend the text as follows "In case of a change to the immediate packaging of an ~~sterile~~ active substance (sterile or not) the following approach may be considered as acceptable: Comparative stability data are required using accelerated and long term testing conditions of three ~~six~~ months duration on at least 2 pilot scale batches of the active substance."	which are excluded from the scope of this GL), therefore the word "sterile" can not be deleted. Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation (sterile active substances).
92.	165-169	4 (EGA)	**Comment:** Please refer to EGA comment to line 126 regarding timing for submission of stability data	Not accepted See outcome on EGA comment on line 126
93.	165-169	6 (IFAH)	***6.4. Change in immediate packaging of the active substance (B.I.c.1.b)*** **Comment:** similarly to line 127-135 this section should provide appropriate conditions where the proposed packaging material is at least equivalent to the approved material in respect of its relevant properties. **Proposed change to lines 168-169**: "Comparative stability data are required using accelerated and long term testing conditions of six months duration (<u>or 3 months where the proposed packaging material is at least equivalent to the approved material in respect of its relevant properties</u>) on at least 2 pilot scale batches of the active substance.	Not accepted See outcome on IFAH comment lines 127 – 135 Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation (sterile active substances).

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
94.	166-169	11 (EGGVP)	**Comment:** It seems to make no sense that requirements for the change in primary packaging of a sterile active substance are much more stringent than those for non-sterile substances. According to the variation guideline, the suitability of the packaging material should be confirmed on 3 months stability data results on at least two pilot scale batches. The same approach should be applicable for sterile products, even if the type of the change is different.	Not accepted Also the "Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures" differentiates between sterile (Type II) and non-sterile active substances (usually Type IA or IB). E.g., the sterilisation of the active substance in the container may have an impact on the stability.
95.	170	3 (EFPIA)	**Comment:** the point covers only the variation type B.II.a.3.b.2 and no indications are given for variations type B.II.a.3.b.4 and B.II.a.3.b.5 **Question:** do these specific variations need to be included (type B.II.a.3.b.4 and B.II.a.3.b.5) or not? If included, then specific wording will be required to explain how and when included.	Not accepted. These are no widely encountered cases of type II variations with stability relevance (Variations type B.II.a.3.b.4 (new excipient --> assessment of viral safety /TSE) and B.II.a.3.b.5 (excipient --> bioequivalence study)); no need to include these type II variations in this GL.
96.	170	3 (EFPIA)	**Comment:** Need to be consistent with Variations Classification guideline. **Proposed change:** "6.5. Change in composition (excipients)	Partly accepted The title of this variation will be changed in accordance with the revised variations classification guideline

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			of the finished product. Qualitative or quantitative composition changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product. (B.II.a.3.b.2)"	
97.	170, 179	10 (Takeda)	**Comment:** 1) What is the definition of a change in composition? 2) Grade changes should be considered 3) supplier changes to be included **Proposed change:** 1) Use **SUPAC-MR**: Modified Release Solid. Oral Dosage Forms. Scale-Up and Postapproval Changes: Chemistry,. Manufacturing, and Controls. This guidance gives exact % w/w quantities of composition changes. 2) Grades of excipients should be considered. 3) material passes all incoming raw material checks and has been audited. Is stability required? New section should state whether or not.	Not accepted Variations are directly linked to type II variations in the EU variations classification guideline; FDA concepts are not applicable
98.	170-218	6 (IFAH)	***Finished product: sections 6.5, 6.6, 6.7, 6.8 and 6.9*** **Comment:** similarly to line 127-135, this section should provide appropriate conditions where the proposed packaging material is at least equivalent to the approved material in respect of its relevant properties. **Proposed change:** for (veterinary) conventional dosage forms and when the active substance is known to be stable,	Not accepted See IFAH comment lines 127 – 135

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			comparative stability data, ~~6~~ 3 months duration, long term and accelerated testing conditions, on ~~two~~ 1 pilot scale batch are required.	
99.	171	3 (EFPIA)	**Comment:** Please specify which ones **Proposed change:** In case of major changes in composition of the finished product which result in a Type II application…	Accepted Heading will be changed in accordance with the revised variations classification GL
100.	171-178 6.5. Change in compositi on of the finished product	7 (PHARMIG)	**Comment:** Since this type of variation refers to 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, it does not make sense to refer to the stability of the active substance. Therefore only quality characteristics of the finished product should be taken into consideration. **Proposed change:** In case of a change in the composition of the finished product, the following approaches may be considered as acceptable: If the quality characteristics of the finished product are changed in such a way that it may impact the stability of the finished product, additional stability data on the finished product, may be required: For conventional dosage forms (e.g. conventional release solid dosage form, solutions) ~~and when the active substance is known to be stable, comparative~~ stability data, 6 months duration, long term and accelerated testing conditions on two	Not accepted Already covered by the title of this type II variation The stability of the active substance in a finished product may be influenced by

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			pilot scale batches are required. For critical dosage forms (e.g. prolonged release form) ~~or when the active substance is known to be unstable, comparative~~ stability data, 6 months duration long term and accelerated stability testing conditions on three pilot scale batches are required.	excipients (e.g., antioxidants), therefore the stability of the active substance (stable / unstable) should be included.
101.	173 – 178	1 (AESPG)	**Comment:** Line 173 & 176: A list or examples, or cross reference to an existing list of conventional and critical dosage forms would be useful to assess criticality. Line 174 – 175: Proposal for conventional dosage forms:"6 months duration long term and accelerated testing conditions on two pilot scale batches are required" to be replaced by: "**three** months duration long term and accelerated testing conditions on two pilot scale batches at least are required" For accelerated testing see comments on line 106-112 above. **Proposed change:** It is proposed to add in line 175 and line 178: "**For herbal drugs, herbal preparations and related herbal medicinal products, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product."**	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines (Decision at 63 QWP). Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation. Not accepted Exception only for herbal substances and herbal preparations
102.	173-178 Type II	4 (EGA)	**Comment:** The draft text refers to	Accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	Variations Change in compositi on of the finished product (B.II.a.3. b.2)		"-For conventional dosage forms and when API is known to be stable : 6M on 2x pilot scale -For critical dosage forms or when API is known to be unstable: 6M on 3x pilot scale" This appears to be in contradiction of requirements as stated in CPMP/QWP/122/02 'Stability Testing of Existing Active Ingredients and Related Finished Products ' (page 10 Section 2.2.3) which reads: 'For critical dosage forms or when the active substances are known to be unstable, stability data on three primary batches are to be provided. **Two of the three batches should be of at least pilot scale, the third batch may be smaller**.' There is no justification for having different requirements for new or variation applications. **Proposed change:** The EGA proposes to align the final text on the existing CPMP/QWP/122/02 requirements. "For conventional dosage forms (e.g. conventional release solid dosage form, solutions) and when the active substance is known to be stable, comparative stability data, 6 months duration, long term and accelerated testing conditions on two pilot scale batches are required. For critical dosage forms (e.g. prolonged release form) or when the active substance is known to be unstable, comparative stability data, 6 months duration long term and accelerated stability testing conditions on three ~~**pilot scale**~~ batches are required. **Two of the three batches should be of at least pilot scale, the third batch may be smaller**."	See also comments 107, 124, 144 Proposal: …. 6 months duration long term and accelerated stability testing conditions on at least three primary batches are recommended. Two of the three batches should be at least pilot scale, the third batch may be smaller.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
103.	173-178	4 (EGA)	**Comment:** Please refer to EGA comment to line 126 regarding timing for submission of stability data.	Not accepted See outcome of EGA comment on line 126
104.	173-176 182 193-196 206-209	2 (APIC/Cefic)	**Comment:** The terms "conventional dosage forms" and "critical dosage forms" should be defined in a Glossary. **Proposed change:** Add Glossary	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines. See also General comment 3
105.	174, 175, 178, 184, 191, 194, 208	3 (EFPIA)	**Comment:** Propose to add and/or for conditions as written it implies that both conditions are absolutely needed for 6 months **Proposed change:** "long term and **/ or** accelerated testing conditions on at least pilot scale for two batches are required"	Partly accepted "or" not acceptable, long term testing is needed. Footnote added after accelerated (*according to ICH/VICH conditions; where appropriate; intermediate storage conditions, if applicable)
106.	174, 177, 183, 194, 197, 207, 210, 218	11 (EGGVP)	**Comment:** EGGVP would like to know the reasons that justify the need for 6 months of stability data before the stated Variations may be applied for. EGGVP proposes 3 months of stability data and a commitment that the stability study will be finalized, and that data will be provided to the authorities, immediately if out of specifications or potentially out of specifications (with proposed action). This should be enough guarantee that quality, safety and efficacy are ensured as well.	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.
107.	176-178, 182-184,	9 (Science)	**Comment:** In some cases there is only possibility to manufacture drug	Not accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	196-198, 209-211		product in production scale, two such batches should be enough for stability studies. **Proposed change:** For critical dosage forms (e.g. prolonged release form) or when the active substance is known to be unstable, comparative stability data, 6 months duration long term and accelerated stability testing conditions on two batches of production scale or three batches of at least pilot scale are required.	Data basis in case of two batches seems not to be sufficient.
108.	176, 182, 196	3 (EFPIA)	**Comment:** Replace word "prolonged" with "modified". Proposed change: Amend For critical dosage forms (e.g. modified release form)	Accepted
109.	177	3 (EFPIA)	**Comment:** The nature of the changes which result in the Type II classification may not necessarily compromise stability. It is suggested that some flexibility could be introduced. **Proposed change:** Add: Where the change is not expected to compromise stability, and where emerging data indicate that it does not do so, submission with 3 months' data may be acceptable.	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.
110.	179	3 (EFPIA)	**Comment:** Consistency with Variations Classification guideline needed. **Proposed change:** 6.6. Change in coating weight of oral gastro-resistant, modified	Accepted Heading will be changed in accordance with the revised variations classification GL,

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			or prolonged release pharmaceutical dosage forms where the coating is a critical factor for the release mechanism. (B.II.a.4.b)	
111.	179-184 Type II Variations Change in coating weight of oral dosage forms (B.II.a.4. b)	4 (EGA)	**Comment:** Please refer to EGA comment to line 126 regarding timing for submission of stability data.	Not accepted See outcome of EGA comment on line 126
112.	180	3 (EFPIA)	**Comment:** Please specify **Proposed change:** In the case of a change in the coating weight of oral dosage forms where the coating is a critical factor for the release mechanism,	Partly accepted Heading will be changed in accordance with the revised variations classification GL.
113.	180-184 6.6. Change in coating weight of oral dosage forms	7 (PHARMIG)	**Comment:** Since this type of variation refers to gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism, it does not make sense to refer to the stability of the active substance. **Proposed change:** In case of a change in the coating weight of oral dosage forms,	Partly accepted Proposal: "Comparative stability data, 6 months duration long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of the three batches should be at least pilot scale, the third batch may be

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			the following approaches may be considered as acceptable: If the quality characteristics of the finished product are changed in such a way that it may impact the stability of the finished product, additional stability data on the finished product, may be required: For critical dosage forms (e.g. prolonged release form) ~~or when the active substance is known to be unstable, comparative~~ stability data, 6 months duration long term and accelerated stability testing conditions on three pilot scale batches are required.	smaller." The coating weight may be a critical factor for the stability of the active substance in a finished product (e.g., water permeability) therefore the concept (stable / unstable active substance) should be kept.
114.	182	3 (EFPIA)	**Comment:** As this type II change only applies to critical dosage forms, the first condition is superfluous, and the second misleading, because changes to non-critical dosage forms are already governed by the variations guideline (3 months' data). **Proposed change:** In the case of a change in the coating weight of a modified release dosage form where the coating is a critical factor for the release mechanism, the following approach may be considered as acceptable: Where the active substance is known to be stable (….3 months' data…. should be provided) Where the active substance is known to be unstable, and/or the emerging stability data indicate that the change may compromise the stability profile (….6 months' data….).	Partly accepted See PHARMIG comment above
115.	183-184 Type II Variations	4 (EGA)	**Comment:** Same comment as EGA comment to lines 173-178 above. There is no justification for having different requirements for	Accepted See also comments 95, 124, 144

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	Change in coating weight of oral dosage forms (B.II.a.4. b)		new or variation applications. **Proposed change:** The final text should read: "For critical dosage forms (e.g. prolonged release form) or when the active substance is known to be unstable, comparative stability data, 6 months duration long term and accelerated stability testing conditions on three ~~pilot scale~~ batches are required. Two of the three batches should be of at least pilot scale, the third batch may be smaller."	Proposal: …. 6 months duration long term and accelerated stability testing conditions on at least three primary batches are recommended. Two of the three batches should be of at least pilot scale, the third batch may be smaller.
116.	184	1 (AESPG)	**Comment:** For accelerated testing see comments above. **Proposed change:** It is proposed to add in line 184: "**For herbal drugs, herbal preparations and related herbal medicinal products, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product."**	Not accepted Exception only for herbal substances and herbal preparations
117.	184	3 (EFPIA)	**Comment:** Need to take into account the nature of the change as well. **Proposed change:** Insert the following text after line 184: "The nature of the change should be taken into account, and should the change not impact stability, a justification or risk based rationale should be provided for the change, with a commitment to perform stability in parallel to the change."	Not accepted This is for Type II variations; in justified cases other approaches may be possible (see introduction).

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
118.	185	3 (EFPIA)	**Proposed change:** 6.7. Change in the manufacturing process of the finished product • B.II.b.3.b, Substantial changes in the manufacturing process of the finished product that may have a significant impact on the quality, safety and efficacy of the medicinal product, • B.II.b.3.b, Introduction of a non-standard terminal sterilisation method B.II.b.3d-e Introduction or increase in the overage that is used for the active substance	Partly accepted The title of this variation will be changed in accordance with the revised variations classification guideline
119.	185	4 (EGA)	**Comment:** This guideline revision triggers questioning on the understanding of the concept of 'complex manufacturing processes'. Although the present guideline might not be the appropriate document to tackle it, the EGA would like to highlight that the current CMDh Q&A question 3.14 does not help clarify the matter and that experience shows interpretations vary. We take the opportunity of the present public consultation to highlight the need for a harmonised understanding of what "complex manufacturing processes are" in order to secure that all guidance documents referring to this concept are implemented consistently and that applicants have a better predictability of regulatory acceptance of their applications.	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines (Decision at 63 QWP).
120.	185-198	4 (EGA)	**Comment:** Please refer to EGA comment to line 126 regarding timing for	Not accepted See outcome of EGA comment on line 126

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			submission of stability data.	
121.	187	3 (EFPIA)	**Comment:** Please specify. **Proposed change:** In the case of changes to the manufacturing process of the drug product which result in a Type II variation ……	Partly accepted Heading will be changed in accordance with the revised variations classification GL
122.	187-198 6.7. Change in the manufacturing process of the finished product	7 (PHARMIG)	**Comment:** Since this type of variation refers to substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product, it does not make sense to refer to the stability of the active substance. Therefore only quality characteristics of the finished product should be taken into consideration. **Proposed change:** In case of variations to the manufacturing process of the drug product, the following approaches may be considered as acceptable: If the quality characteristics ~~(e.g. physical characteristics, impurity profile)~~ of the finished product ~~active substance or an excipient~~ are changed in such a way that stability may be compromised, ~~comparative~~ stability data are required in accelerated and long term testing conditions, on the drug product before and after the change: For conventional dosage forms (e.g. conventional release solid dosage form, solutions) ~~and when the active substance is known to be stable, comparative~~ stability data, 6 months	Partly accepted Proposal mainly agreed comparative stability should be available The manufacturing process may be a critical

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			duration, long term and accelerated testing conditions on two pilot scale batches are required. For critical dosage forms (e.g. prolonged release form~~) or when the active substance is known to be unstable, comparative~~ stability data, 6 months duration long term and accelerated stability testing conditions on three pilot scale batches are required.	factor for the stability of the active substance in a finished product (e.g., heat labile active substance) therefore the concept (stable / unstable active substance) should be kept.
123.	189-190 Type II Variations Change in manufacturing process of the finished product (B.II.b.3.b, B.II.b.3.d-e)	4 (EGA)	**Comment:** The second paragraph (lines 189 and 190) appears to be misplaced as there is no relationship between a change in the manufacturing process of the finished product and the actual contents of the 2nd paragraph. **Proposed change:** Please delete the 2nd paragraph.	Partly accepted (rephrasing – no deletion) "If the quality characteristics (e.g. impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the change"
124.	189-192	2 (APIC/Cefic)	**Comment:** Section 6.7 relates to changes in the manufacturing process of the finished product. However, these lines relate to changes of the quality characteristics of the active substance or of an excipient. We do not see any relationship of this with the heading of this section. **Proposed change:** Rewrite the section to make it consistent.	Accepted "If the quality characteristics (e.g. impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Possibly the words "the active substance or an excipient" should be changed into: "finished product"?	change"
125.	189-192, 202-205	3 (EFPIA)	**Comment:** It is unclear why changes in quality characteristics of an API or excipient are foreseen as an outcome of process changes in drug product manufacture. If such changes were to be made, they would be handled under their own appropriate change categories. Should it read drug product instead of active substance and excipient? **Proposed change:** Please clarify. Is this a typo?	Accepted "If the quality characteristics (e.g. impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the change"
126.	189-192, 202-205	9 (Science)	**Comment:** These four lines of text are not related to variations "Change in the manufacturing process of the finished product (B.II.b.3.b, 3.d-e)" or "Change in the batch size of the finished product (B.II.b.4.d)" respectively and seem to be included by mistake and should be deleted.	Accepted "If the quality characteristics (e.g. impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the change"
127.	189-190, 202-203	1 (AESPG)	**Comment:** If the manufacturing process of the finished product is changed or if the batch size of the finished product is changed the quality characteristics of the active substance or excipient should not change. **Proposed change:** Wording in chapters 6.7 and 6.8 should be adapted accordingly.	Accepted "If the quality characteristics (e.g. impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
				change"
128.	189-192 & 202-205	1 (AESPG)	**Comment:** It is unclear as to why reference to the change of quality characteristics of the active substance or an excipient is made in this chapter. **Proposed change:** We believe this is an error and should be removed. Alternatively "finished medicinal product" should replace "active substance and excipient".	Accepted "If the quality characteristics (e.g. impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the change"
129.	189-190	11 (EGGVP)	**Comment:** EGGVP proposes to expand the text in order to reflect not only the quality of the active substance and excipients, but also of the manufacturing process itself. **Proposed change:** "…..of the active substance, or an excipient, or final product due to change in the manufacturing process are changed….."	Partly accepted The sentence is rephrased and reference is made to the finished product.
130.	193, 197	3 (EFPIA)	**Comment:** For conventional dosage forms containing stable drug substance, a default expectation of 6 months' data to support manufacturing process changes is considered excessive. **Proposed change:** Reduce to 3 months. If desired, add "If the emerging stability data indicate there may be deterioration in the stability profile, 6 months' data will be required for submission".	Not accepted Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.
131.	193-198	1 (AESPG)	**Comment:**	Not accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Line 194-195: Proposal for conventional dosage forms:"6 months duration long term and accelerated testing conditions on two pilot scale batches are required" to be replaced by: "three months duration long term and accelerated testing conditions on two pilot scale batches at least are required". For accelerated testing see comments on line 106-112 above. **Proposed change:** It is proposed to add in line 195 and 198: "**For herbal drugs, herbal preparations and related herbal medicinal products, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product."**	Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation. Not accepted Exception only for herbal substances and herbal preparations
132.	196 Type II Variations Change in the batch size of the finished product (B.II.b.4. d)	4 (EGA)	**Comment:** The variation guideline excludes immediate release formulations as type II change. For this reason the clarification of terms (such as prolonged release form) should be added. **Proposed change:** Please clarify the reference to "prolonged release dosage form".	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines.
133.	196-198 Type II Variations Change in	4 (EGA)	**Comment:** Same comment as EGA comments to lines 173-178 and 183-184 above. There is no justification for having different requirements for	Partly accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	manufacturing process of the finished product (B.II.b.3.b, B.II.b.3.d-e)		new or variation applications. **Proposed change:** The final text should read: "For critical dosage forms (e.g. prolonged release form) or when the active substance is known to be unstable, comparative stability data, 6 months duration long term and accelerated stability testing conditions on three ~~**pilot scale**~~ batches are required. **Two of the three batches should be of at least pilot scale, the third batch may be smaller."**	See comments 95, 107, 144 Proposal: …. 6 months duration long term and accelerated stability testing conditions on at least three primary batches are recommended. Two of the three batches should be at least pilot scale, the third batch may be smaller.
134.	198	3 (EFPIA)	**Comment:** Consideration should be given to situations where changes to the manufacturing process are introduced to improve the overall stability of the finished product. **Proposed change:** Insert the following text after line 198: "Should the change in the manufacturing process be performed to encourage an improvement in the overall stability of the finished product, suitable data should be presented or a rationale should be given for not performing stability. "	Not accepted. How to define an improvement of the overall stability (e.g. is introduction of an overage an improvement of the overall stability?)
135.	199	3 (EFPIA)	**Proposed change:** "6.8 Change in the batch size (including batch size ranges) of the finished product for pharmaceutical forms manufactured by complex manufacturing processes, (not applicable to standard immediate release oral pharmaceutical forms or non-sterile liquid based pharmaceutical forms).	Partly accepted Heading will be changed in accordance with the revised variations classification GL
136.	199-211	4 (EGA)	**Comment:**	Not accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	Type II Variations Change in the batch size of the finished product (B.II.b.4. d)		Please refer to EGA comment to line 126 regarding timing for submission of stability data.	See outcome of EGA comment on line 126
137.	200	3 (EFPIA)	**Comment:** Please specify what types of changes. **Proposed change:** In the case of variations to batch size of the drug product resulting in a Type II variation, and if the quality characteristics (e.g. ….) of the drug product are changed …….	Partly accepted Heading will be changed in accordance with the revised variations classification GL, then this will be clearer specified
138.	200-211 6.8. Change in the batch size of the finished product	7 (PHARMIG)	**Comment:** Since this type of variation refers to changes in the batch size of the finished product, it does not make sense to refer to the stability of the active substance. Therefore only quality characteristics of the finished product should be taken into consideration. **Proposed change:** In case of variations to the batch size of the drug product, the following approaches may be considered as acceptable: If the quality characteristics ~~(e.g. physical characteristics, impurity profile)~~ of the finished product ~~active substance or an~~	Partly accepted "If the quality characteristics (e.g, impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the change"

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			~~excipient~~ are changed in such a way that stability may be compromised, ~~comparative~~ stability data are required in accelerated and long term testing conditions, on the drug product before and after the change: For conventional dosage forms (e.g. conventional release solid dosage form, solutions) ~~and when the active substance is known to be stable, comparative~~ stability data, 6 months duration, long term and accelerated testing conditions on two pilot scale batches are required. For critical dosage forms (e.g. prolonged release form) ~~or when the active substance is known to be unstable, comparative~~ stability data, 6 months duration long term and accelerated stability testing conditions on three pilot scale batches are required.	comparative stability should be available The batch size may be a critical factor for the stability of the active substance in a finished product (e.g., longer light exposure if batch size is increased in case of light sensitive active substance); therefore the concept (stable / unstable active substance) should be kept.
139.	200-211	11 (EGGVP)	Comment: A change in the batch size does not necessarily imply a change in the product quality or a change in the manufacturing process (unless the reactor is changed). According to EGGVP's opinion, delivering the manufacturing process validation and comparing the validation results obtained with the two batches would be sufficient.	Not accepted Normally changes in the batch size are classified as a type IA or a type IB variation. However, this type II variation refers to pharmaceutical forms manufactured by complex manufacturing processes.
140.	202-205 Type II Variations Change in the batch size of the	4 (EGA)	**Comment:** Same comment as EGA comment to lines 189 and 190. The second paragraph (lines 202 to 205) appears to be misplaced as there is no relationship between a change in the batch size of the finished product and the actual contents of the 2nd paragraph.	Partly accepted Rephrased to: "If the quality characteristics (e.g, impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	finished product (B.II.b.4. d)		**Proposed change:** Please delete the 2nd paragraph	accelerated and long term testing conditions, on the finished product before and after the change"
141.	202-205	5 (Hikma)	**Comment:** The reference to the active substance or an excipient eventual changes doesn't seem adequate, since it's unlikely this to happen, when do finished product scale-up. **Proposed change:** "If the quality characteristics (e.g. physical characteristics, impurity profile) of the finished product are changed in such a way that stability may be compromised..."	Accepted "If the quality characteristics (e.g, impurity profile) of **the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the change"
142.	202-211	2 (APIC/Cefic)	**Comment:** Section 6.8 relates to changes in the batch size of the finished product. However, these lines relate to changes of the quality characteristics of the active substance or of an excipient. We do not see any relationship of this with the heading of this section. **Proposed change:** Rewrite the section to make it consistent. Possibly the words "the active substance or an excipient" should be changed into: "finished product"?	Accepted "If the quality characteristics (e.g, impurity profile) **of the finished product** are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the finished product before and after the change"
143.	206-208	1 (AESPG)	**Comment:** Changes in batch size for conventional dosage forms are covered under B.II.b.4.a and e in the EC guideline on the categories of variations. But conventional dosage forms are also mentioned in this draft guideline (section 6.8 Change in the batch size of the finished product B.II.b.4.d): what is the	Partly accepted This Type II variation covers changes relating to all other pharmaceutical forms manufactured by complex manufacturing processes - No need to define criteria for conventional dosage forms

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			difference between the "conventional dosage forms" described in line 206-208 and the changes described in B.II.b.4a and e? **Proposed change:** A more precise description of the dosage forms that belong to this section or deletion of lines 206-208.	(conventional immediate release oral pharmaceutical forms = IA; more than 10-fold = IB for immediate release (oral) pharmaceutical forms) For example, sterile products are not covered by B.II.b.4a and e. Examples for complex processes are given in Annex II to the NfG on Process Validation (e.g., lyophilisation) Proposal: For conventional dosage forms manufactured by a complex manufacturing process and when the active substance is known to be stable, comparative stability data, 6 months duration, long term and accelerated testing conditions on at least two batches of at least pilot scale are recommended.
144.	206-208	3 (EFPIA)	**Comment***:* B.II.b.4.d covers changes related to all other pharmaceutical forms manufactured by complex manufacturing processes. Therefore B. II.b.4.d is not applicable to changes to standard immediate release oral pharmaceutical forms or non-sterile liquid based pharmaceutical forms. **Proposed change***:* Delete lines 206 - 208. Or Section would benefit from a rethink of the intentions, and should be restricted to Type II changes.	Partly accepted See above

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
145.	206-208	5 (Hikma)	**Comment:** considering the scale-up, stability data on pilot batches doesn't provide any additional information on what was originally submitted, i.e. pilot batches. **Proposed change:** "For conventional dosage forms (e.g. conventional release solid dosage form, solutions) and when the active substance is known to be stable, comparative stability data, 6 months duration, long term and accelerated testing conditions on 1 production scale batch are required."	Partly accepted Will be rephrased to "at least two batches of at least pilot scale".
146.	206-211	1 (AESPG)	**Comment:** Some companies, when preparing a variation to change the batch size, manufacture production scale batches but very seldom pilot scale batches. The type IA variation requires batch data on one production scale batch. The guideline should hence leave the possibility to use production scale batches instead of pilot scale only. For accelerated testing see comments on line 106-112 above. **Proposed change:** The same wording that in the above sections should be used i.e. "at least pilot scale". Lines 207-208: Proposal for conventional dosage forms :"6 months duration long term and accelerated testing conditions on two pilot scale batches are required" to be replaced by: "three months duration long term and accelerated testing conditions on two pilot scale batches at least are required"	Partly accepted Will be rephrased to "at least two batches of at least pilot scale". Minimum of 6 months stability data at time of submission are considered to be reasonable for this type of variation.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Please add in line 208 and line 211: "**For herbal drugs, herbal preparations and related herbal medicinal products, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product.**"	Not accepted Exception only for herbal substances and herbal preparations
147.	208, 211	3 (EFPIA)	**Comment:** Clarity is needed on the term pilot scale here. Is this for batches manufactured outside of the Type IA and B criteria? If performing at production scale how many supporting batches are required/need to be placed on stability? Is a stability study on one batch sufficient?	Partly accepted This is only for Type II variations according to B.II.b.4.d Will be rephrased to "at least two batches of at least pilot scale" and "at least three primary batches are recommended. Two of the three batches should be a least pilot scale, the third batch may be smaller""
148.	209	3 (EFPIA)	**Comment:** Critical dosage forms are listed here. For clarity do other dosage forms need to be listed here as well e.g. creams, suspensions?	Not accepted. A full list of critical dosage forms can not be provided.
149.	209 Type II Variations Change in the batch size of the	4 (EGA)	**Comment:** The variation guideline excludes immediate release formulations as type II change. For this reason the clarification of terms (such as prolonged release form) should be added. **Proposed change:** Please clarify the reference to "prolonged release dosage form".	Not accepted A glossary seems not to be necessary for this guideline; terms should be defined in other relevant guidelines

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	finished product (B.II.b.4. d)			
150.	209-211	5 (Hikma)	**Comment:** considering the scale-up, stability data on pilot batches doesn't provide any additional information on what was originally submitted, i.e. pilot batches. **Proposed change:** "For critical dosage forms (e.g. prolonged release form) or when the active substance is known to be unstable, comparative stability data, 6 months duration long term and accelerated stability testing conditions on 1 (or 2) industrial scale batches are required."	Partly accepted Will be rephrased to "at least three primary batches are recommended. Two of the three batches should be at least pilot scale, the third may be smaller."
151.	211 Type II Variations Change in the batch size of the finished product (B.II.b.4. d)	4 (EGA)	**Comment:** The specific change of 'batch size increase' should be addressed in this section. For such changes, applicants will usually rely on stability data from commercial batches (large size). From a commercial perspective, consideration should be made of the fact that a strict requirement of three batches will imply that a vast majority of the batches concerned might remain unused by patients and might need to be destroyed as the conjunction of long variation procedures, size of the market served and expiry date of some the finished product. In such justified cases, the same approach as that applicable for Type IB variations should apply i.e. data should be provided for one commercial batch and a commitment to include the subsequent 2 commercial batches in stability programmes (when justified).	Not accepted This type II variation only refers to variations with a complex manufacturing process.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: Please introduce a reference to the specific situation of increased batch size as referred above.	
152.	212	3 (EFPIA)	**Proposed change:** 6.9 Change in immediate packaging of the finished product • (B.II.e.1a.3. change in qualitative and quantitative composition of the immediate packaging for Sterile medicinal products) • (B.II.e.1a.4.) changes to a less protective pack, where there is a reduction in shelf life or storage conditions (B.II.e.1.b. 2.) change in the type if sterile medicinal product container	Partly accepted Heading for this variation will be changed in accordance with the revised variation classification guideline
153.	212-218	1 (AESPG)	**Comment:** Line 216: For product categories not per se dictating a Type II category, change to a less protective pack only calls for a Type II variation if it is accompanied by a reduction in shelf-life or a change in storage conditions. Also, that in a situation where there may be a risk of interaction, but this is demonstrated not to be the case, type IB variation may be maintained (e.g. B.II.e.1.a.2) and 3 month data are stated to be adequate. **Proposed change:** Please modify the sentence as follows: "**In the case of a less protective pack where there is an associated reduction in shelf-life or a change in storage conditions, or in cases where there is a risk of interaction between the packaging material and the**	Partly accepted Heading for this variation will be changed in accordance with the revised variation classification guideline

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			content and where it cannot be demonstrated that no interaction occurs (e.g. no migration of components)… For accelerated testing see comments above. **Proposed change:** Please add "*For herbal drugs, herbal preparations and related herbal medicinal products, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage below 25°C is clearly labelled on the product. In the case of more resistant immediate packaging material stability studies can usually be omitted.*"	Not accepted Exception only for herbal substances and herbal preparations
154.	212-218 Type II Variations Change in immediate packaging of the finished product (B.II.e.1.a.3, B.II.e.1.a.4, B.II.e.1.b.2)	4 (EGA)	**Comment:** Unlike for the other variations described, point 6.9 does not make a clear distinction between conventional and critical dosage forms. In addition, the requirements should be aligned on those applicable to new submissions. Refer to EGA comments to lines 173-178 and 183-184 above. There is no justification for having different requirements for new or variation applications. For conventional dosage forms packed in less protective packaging 6 months data (including accelerated data) on 2 batches of the product should be sufficient to assess the suitability of the new packaging, given that the stability characteristics of the product would be well understood through the development process and based on stability data generated on the current immediate packaging configuration.	Partly accepted See comment also 95, 107,124

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: The final text should distinguish between stable and unstable active substances and for the latter read: "For critical dosage forms (e.g. prolonged release form) or when the active substance is known to be unstable, comparative stability data, 6 months duration long term and accelerated stability testing conditions on three ~~**pilot scale**~~ batches are required. **Two of the three batches should be of at least pilot scale, the third batch may be smaller**.""	Proposal "…on at least three primary batches of the finished product. Two of the three batches should be of at least pilot scale, the third batch may be smaller."
155.	212-218	4 (EGA)	**Comment:** Please refer to EGA comment to line 126 regarding timing for submission of stability data.	Not accepted See outcome of EGA comment on line 126
156.	214	3 (EFPIA)	**Comment:** Please specify which changes **Proposed change:** In the case of changes to the immediate packaging which result in a Type II variation……	Partly accepted Heading will be changed in accordance with the revised variations classification GL, then this will be clearer specified
157.	216	3 (EFPIA)	**Comment:** Please note that for products not per se dictating a Type II category, change to a less protective pack only precipitates Type II status if accompanied by reduction in shelf-life or change in storage conditions. Also, that in a situation where there may be a risk of interaction, but this is shown not to be the case, IB status may be maintained (e.g. B.II.e.1.a.2) and 3-month data are stated to be adequate.	Partly accepted Heading will be changed in accordance with the revised variations classification GL, then this will be clearer specified

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: In the case of a less protective pack where there is an associated reduction in shelf-life or change in storage conditions, or in the case where there is a risk of interaction between the packaging material and the content and where it cannot be shown that no interaction occurs (e.g. no migration of components……..), (6 months' data….)	
158.	216-218	3 (EFPIA)	**Comment:** The cases described are unclear relative to the changes listed and described in the EU guideline: -Sterile medicinal products and biological/immunological medicinal products. -The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life. -Sterile medicinal products and biological/immunological medicinal products Does that mean that this requirement applies only for: In the case of less protective packaging or when a risk of interaction occurs, mainly for semi-solid or liquid dosage forms, comparative stability data are required using accelerated and long term testing conditions of six months duration on three pilot batches of the finished product? **Proposed change:** please clarify intentions	Partly accepted Heading will be changed in accordance with the revised variations classification GL, then this will be clearer specified
159.	216-218	9 (Science)	**Comment:** In some cases there is only possibility to manufacture the drug product in production scale, two batches should be enough for presentation stability results.	Not accepted Data basis in case of two batches seems not to be sufficient

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: In the case of less protective packaging or when a risk of interaction occurs, mainly for semi-solid or liquid dosage forms, comparative stability data are required using accelerated and long term testing conditions of six months duration on three pilot batches or two production batches of the finished product.	
160.	216-218	11 (EGGVP)	**Comment:** The risk of interaction is only relevant when the material in contact with the finished product has been changed; if this is not the case, stability data should not be required. Furthermore, it makes no sense that requirements for new packaging (3 batches) are more stringent than for initial applications (2 batches for conventional dosage forms at the date of submission according to th e *Note for Guidance on Stability testing of existing active substances and related finished products* EMEA/CVMP/846/99).	Not accepted The guidelines reads "… or when the risk of interaction occurs …" This has to justified. Partly accepted Rephrased to "Two of the three batches should be at least pilot scale; the third batch may be smaller.
161.	218	3 (EFPIA)	**Comment:** Consideration should be given to the appropriate stability requirements when an equivalent packaging material is used. **Proposed change:** Insert the following statement: "A stability commitment or 3 months stability on 2 batches of at least pilot scale should be provided on application should an equivalent packaging material be used. "	Not accepted This change mainly focus on changes to less protective packaging materials Minimum of 6 months stability data on at least 3 primary batches at time of submission are considered to be reasonable for this type of variation.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
162.	221	10 (Takeda)	**Comment:** Does this mean that 6 months of data is needed before release? **Proposed change:** Clarify expectations depending on type of change	Not accepted Line 220 refers to Type IA and IB variations that require stability data on the finished product It does not mean that 6 months stability data are needed before release. However, adequate follow-up studies on commitment batches have to be performed.
163.	222-223	1 (AESPG)	**Comment:** If full scale batch stability data are available at the submission time of the variation, the requirement for placing the first production scale batch on long term stability should not be necessary.	Not accepted. Already covered in lines 222 – 225 ("unless it has already been submitted as part of the variation application")
164.	222-228	3 (EFPIA)	**Comment:** "For Type IA, IB and Type II variations that require the generation of stability adequate follow up studies need to be performed." With respect to studies that need to be performed, we believe that it should only be necessary to perform testing on those parameters impacted by the change (non-critical or non-stability indicating tests, not relevant to the change or impacted by the change, can be performed optionally throughout study, or at the end of the study and not at every time point.). This is particularly relevant for well understood and controlled processes e.g. those developed via a QbD approach. **Proposed change:** For all Type IA and IB variations that require the generation of stability data on the finished product, adequate follow up studies on commitment batches need to be performed.	Not accepted There are specific recommendations for QbD approaches.

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			For all Type II variations that require the generation of stability data on the finished product, at least the first production scale batch manufactured according to the approved variation should be placed on long term stability testing using a stability testing protocol deemed appropriate for the change, or as described in the original application unless it has already been submitted as part of the variation application. Stability studies need to be continued to cover the entire shelf-life.	Addition of "using a stability testing protocol deemed appropriate for the change" not acceptable.
165.	227-228 Commitment batches	4 (EGA)	**Comment:** The draft text includes a requirement for applicant to notify the authorities of any problems or out of specifications appearing in the stability programme regardless of the potential risk or impact on the stability programme outcome. The EGA proposes that only those OOS that are compromising the stability programme outcome as presented in the variation application should be notified. This would streamline resources and secure a strong focus on where the risk is. The complete overview of OOS would be available for inspections).	Not accepted All OOS results in commitment batches should be notified to authorities. This is in line with the Classification GL where for other types of variations the OOS results have to be provided to the competent authorities.
166.	227-228	6 (IFAH)	**Comment:** authorities should only be informed when outside specification results are obtained. As well as being informed only when problem is significant enough to impact the outcome of the study. **Proposed change:** "The results of these stability studies	Partly accepted Proposal: The results of these stability studies

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			should be made available on request and the authorities should be informed ~~if any problems appear with the stability studies~~ of any outside specification or a change made to the stability study that could impact the outcome of the study as described in the variation".	should be made available on request and the authorities should be informed if any problems appear with the stability studies (e.g., any out of specification results).
167.	229 **References**	1 (AESPG)	**Comment:** In the references the guidelines reflecting specific features of herbal drugs, herbal preparations and related herbal medicinal products are missing. **Proposed change:** We propose to add: Guideline on quality of herbal medicinal products / traditional herbal medicinal products (EMA/CPMP/QWP/2819/00 Rev. 2; EMA/CVMP/814/00 Rev. 2; EMA/HMPC/201116/2005 Rev. 2), Gguideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products / traditional herbal medicinal products (EMA/CPMP/QWP/2820/00 Rev. 2; EMA/CVMP/815/00 Rev. 2; EMA/HMPC/162241/ 2005 Rev. 2), Guideline on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/214969/2006), Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/CHMP/2124869/2006), Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products (EMA/HMPC/3626/2009),	Partly accepted General Guidelines are added (see General requirements)

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Guideline on Markers used for quantitative and qualitative analysis of Herbal Medicinal Products and traditional Herbal Medicinal Products (EMA/HMPC/253629/2007).	
168.	231	9 (Science)	**Comment:** inappropriate reference to the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products **Proposed change:** replace "OJ L 334, 12.12.2008, p. 7" with "2010/C 17/01".	Partly agreed This reference is changed according to the revised variations classification GL
169.	234	6(IFAH)	**Comment:** The reference should read GL3 instead of GL43.	Accepted
170.	244-245 **Annex I**	1 (AESPG)	**Comment:** The definition of stable and unstable active substances does not reflect the special requirements for herbal preparations as intermediate and accelerated testing is usually not requested. The definition should therefore be amended for herbal drugs and herbal preparations used as active substances. **Proposed change:** It's proposed to add: "**A herbal drug or herbal preparation used as active substance is considered as stable if it is within the initial specification when stored at 25°C/60 % RH (2 years).**"	Not accepted Not in line with basic guidelines
171.	244-245	8 (PolyPeptide)	**Comment:**	Not accepted

	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			The proposed text does not take into account the long term storage condition of the drug substance in question. It is very common for drug substances (e.g. peptides) to be stable at 5°C or -20°C but unstable at higher temperature. We consider drug substances with defined long term storage in refrigerator (5°C ± 3°C) or freezer (-20°C ± 5°C) as stable at their defined storage conditions. We would therefore propose Annex I to be more elaborated to cover also storage in refrigerator and freezer. **Proposed change:** An active substance is considered as stable if it is within the initial specifications when stored at any of the following conditions • 25°C/60% RH or 30°C/65% RH, respectively, (2 years) and 40°C/75% RH (6 months) • 5°C (2 years) and 25°C/60% RH (3 moths) • -20°C (2 years) Where 25°C/60% RH, 5°C and -20°C, respectively, is the defined long term storage condition for the drug substance.	The stability of an active substance should not be linked to storage at different temperatures.
172.	**Annex II** 254	3 (EFPIA)	**Proposed change:** Data collected under accelerated conditions can be used as supportive data for extrapolation of shelf-life for the finished product.	Not accepted Proposal already covered by lines 255-256