15 May 2012
EMA/257975/2012
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline for the processing of renewals in the centralised procedure' (EMEA/CHMP/2990/00 Rev.4)

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

Stakeholder no.	Name of organisation or individual
1	EFPIA (European Federation of Pharmaceutical Industries and Associations)
2	Celgene Europe Ltd
3	Gilead Sciences International Limited
4	Elan Pharma International Ltd
5	Sandoz GmbH, Kundl Austria
6	F.Hoffmann – La Roche Ltd
7	Janssen Pharmaceutical Companies of Johnson & Johnson

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	EFPIA appreciates the possibility to comment on this important document. However, the quality of comments could have been improved consequently leading to better usefulness for EMA, if more time would have been allowed for discussion of the draft.	The comment is acknowledged.
1	EFPIA is concerned that the new guideline contains significant new requirements for the renewal documentation, particularly in relation to the Addendum to the Clinical Overview which bears a striking resemblance to the structure and content of the future PSUR as described in the Good Vigilance Practices Guideline; Module VII – PSURs. The new format is based on ICH E2C (R2) guideline currently in Step 2 and hence will also be required in other countries of the world. As a result, such changes in the renewal requirements in the EU will lead to the necessity to create EU-specific Clinical Overviews in future, while for other countries, similar information has to be provided in the format of a PSUR. The Clinical Overview should be a summary of the safety data of the PSUR and not reproduce all these data. Reference to previous PSUR should be sufficient. Also of note are the significant changes in processes, procedures, documentation training and IT systems needed to produce the future PSUR with its focus on benefit risk evaluation. This would apply equally to the information being requested in the new Clinical Overview. Under Article 39 of the draft Commission Implementing Regulation published on 2 April, a six month transition period from 02 July 2012 has been provided for the implementation of (inter alia) the future PSUR i.e. PSUR in the new format would need to be submitted after 01 January 2103. EFPIA therefore proposes that this guideline is given the same transition period in order to accommodate the significant interdependencies between the new renewal requirements and Articles 34 of the Implementing Regulation and Module VII of the GVP Guidelines. i.e. that the new content and format would apply to renewals submitted after 01 January 2013.	The Renewal is a crucial point in the life-cycle of a product, where a re-evaluation of the benefit/risk of the product is performed. PSURs are no longer required as part of the Renewal application. However, a critical discussion on the benefit/risk of the product is needed and consequently it should be provided in the Addendum to the Clinical Overview. The revised Guideline should be followed for renewal submitted as of the 2 July 2012. Comment not accepted. The importance of the pharmacovigilance inspection

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	A further concern is the new requirement to provide a critical assessment of the impact of inspection findings on the benefit/risk balance of the medicinal product. EFPIA does not consider that the wording "critical assessment of the impact of the finding on the benefit/risk balance of the medicinal product" is appropriate in the context of the majority of inspections (particularly of routine inspections) which are mainly focused on **processes and systems** rather than on individual products. As such any critical or major findings relate to "*a deficiency in PV systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines",* i.e. there is not a specific focus on the intrinsic benefit risk of an individual product but on deficiencies in the system Furthermore, inspections which can be product specific are generally those triggered by benefit risk concerns. Proposals to address these concerns are included in the detailed comments section below.	findings is not determined by the reason for which the inspection was initiated (triggered/product specific or routine).
1	As the due date for submission now needs to occur at least 9 months prior to expiry of MA there should be some flexibility in handling of variations during the time of renewal submission and Commission Decision. Some further guidance related to this would be welcomed.	These situations are addressed in the post-authorisation procedural guidance published on the EMA website. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000038.jsp&mid=WC0b01ac0580023e7c&jsenabled=true. MAHs are advised to contact EMA for further guidance on how to handle potential overlapping

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		procedures on a case by case basis.
1	No information is included on the transparency policy regarding the outcome of a Renewal Procedure. EFPIA proposes to include this for sake of completeness. For instance, in cases where the MAH does not submit a renewal application and, consequently, the MA will expire, what will be the agency's communication policy?	In terms of transparency, please refer to section 3.6.4 and 3.6.5 of the Guideline. The EMA communication policy is described in separate documents which are publicly available. The EMA communication policy addresses several procedures and it is not specific on Renewals. Therefore, it is not considered that further guidance on this topic should be included in this Guideline. In case of expiry or non-submission of a renewal application, a public statement at the time of expiry of the marketing authorisation is published. At the same time, the EPAR is marked to show that the marketing authorisation is no longer valid. Please see published

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		Work instruction for "Non-removal of the EPAR following withdrawal/expiry of the Marketing Authorisation": http://www.emea.europa.eu/docs/en_GB/document_library/Work_Instruction_-_WIN/2009/09/WC500003056.pdf Positive renewals result in an update of the EPAR: http://www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2009/09/WC500002911.pdf
1	Furthermore, EFPIA would appreciate clarifications on key procedural aspects, e.g. when will PRAC start to be involved, when will the company be informed of the PRAC rapporteurship allocation, what are the criteria used to define the major safety concerns that precludes PRAC involvement, **why will the company be required to supply responses to LoOIs systematically to all PRAC members**	A systematic involvement of the PRAC Rapporteur is envisaged for all CAPs. The PRAC Rapporteur will also be in charge of drafting the RMP AR in those cases, where a new or updated RMP is submitted. The PRAC will be involved

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		systematically and issue an assessment report/advice. The PRAC Rapporteurship will be described in a separate document, since this is not a procedure specific for Renewals.
1	EFPIA noticed that no information regarding Module 5 is provided in the proposed revision. Therefore EFPIA is wondering whether e.g. an Addendum Report/Line Listing (covering the gap between the previous PSUR and the data lock point) will no longer have to be provided as part of the renewal.	Confirmed. No Addendum Report/Line Listings will be required as part of the renewal in line with the new approach for PSURs.
3	Throughout reference is made to 724/2004 and 2001/83 but not 1235/2010 or 2010/84 despite referencing specific requirements from them and aligned with changes in them such as the pharmacovigilance master file and reference to implementing measures and good Pharmacovigilance practice. Text should be clear that at time of drafting implementing measures referenced are still draft.	Directive 2001/83/EC and Regulation (EC) No 726/2004 remain the valid references. These have to be understood as including all amending legislation which has to come into force. These documents have been modified at several occasions and there is no need to refer to every single amending act.
7	We are concerned that the new guidance requires the EU Clinical Overview to contain information that will also be required in PSURs, thereby confusing the purpose of the two	Not in agreement. The clinical overview should contain sufficient

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	documents. In practice the removal of the requirement to submit a PSUR as part of the Renewal is replaced by having to provide the PSUR information in the EU Clinical Overview, which will add to the companies' administrative burden. Proposed change: We would like EMA to reconsider this approach and allow the Addendum to the Clinical Overview to cross-reference the PSUR.	information as to allow a re-evaluation of the benefit/risk.
7	Whilst we understand the importance of ensuring that all renewals achieve an adopted Commission Decision before the expiry date of the marketing authorisation, the requirement for no variations to the authorisation to be submitted whilst the renewal is being assessed is of significant concern due to the new legal requirement for the renewal application to be submitted nine months before the expiry date. For products where there is significant activity in connection with authorisation updates even after 5 years, some allowances must be made to ensure that MAHs can maintain safety and business priorities and keep the authorisation current and in compliance with obligations. For example, this is recognised in the draft guideline in respect of quality-related changes: "Lines 147-150: Addendum to Quality Overall Summary There is no updating of Part II/Module 3 quality data at renewal. The marketing authorisation holder has an obligation to keep this updated on an on-going basis throughout the life of the product using variation procedures." Proposed change: Therefore, there needs to be flexibility/understanding that essential as well as limited other changes can be submitted during the renewal process. In particular, consideration should be made to	These situations are addressed in the post-authorisation procedural guidance published on the EMA website. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000038.jsp&mid=WC0b01ac0580023e7c&jsenabled=true. MAHs are advised to contact EMA for further guidance on how to handle potential overlapping procedures on a case by case basis.

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	- Allowing variations to update safety / labelling information - Allowing essential and limited CMC changes to be submitted during the renewal process - Allowing submission of specific major variations, provided this is discussed at the pre-renewal submission meeting - Allowing the submission of variations as soon as the CHMP opinion is granted	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 30	1	Comment: While the statement in line 30 is correct and, if no application for MA renewal is submitted, the MA will ”expire by law”, there may be cases when the assessment runs over the expiration date. Proposed change: “In order for a marketing authorisation to remain valid, a renewal is required five years after the granting of the marketing authorisation (irrespective of whether the marketing authorisation is suspended). In the case a MAH does not submit the renewal application; the MA will expire by law five years after the granting of the marketing authorisation. However this principle will not automatically apply where the assessment of a renewal application runs over the expiration date.”	Not in agreement. Provided that the renewal application has been submitted 9-months prior to the expiry date, the Agency will handle the renewal procedure to allow For the Commission Decision to be issued before the expiry date of the MA.
Lines 30 and 62	5	Comment: Redundant information “In the case a MAH does not submit the renewal application, the MA will expire by law. Proposed change (if any): The sentence could be deleted in one of the two sections	Not in agreement.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 41	1	Comment: The draft guidance states that the renewal shall be granted for an unlimited time unless the competent authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal. EFPIA proposes to clarify that exposure encompasses 'global' exposure, not just exposure in patients residing within the EEA.	The text is aligned with the wording of the new pharmacovigilance legislation. Any further clarifications regarding exposure can be found in the "Reflection Paper Criteria for requiring one additional five-year Renewal for Centrally Authorised Medicinal Products", which is referred to in the Renewal GL.
46-47	3	Comment: References assessments and recommendations on EMA portal – is this meant to be per signal detection module? Proposed change (if any): Add cross reference to signal detection module of Good Pharmacovigilance Practice.	It refers to PRAC recommendations, CHMP Opinions or CMD(h) positions in relation to any procedures (e.g. PSURs, Referrals, etc.) and not only signal detection.

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Line 56 – 58	1	Comment: The renewal submission date should be agreed with EMA only, as the Rapporteur/Co-Rapporteur might be very difficult to reach for such a procedural discussion. Proposed change: The marketing authorisation holder should agree in advance the submission date of the renewal application with the EMA ~~and the Rapporteur/Co-Rapporteur~~ taking into account the recommended starting dates published on the EMA website[4] (see also section 3.2)	Comment accepted. The wording has been amended as follows: "…EMA who will liaise with the Rapp/Co-Rapp, as appropriate…"
Line 70	1	Comment: Neither the current text "The EMA will acknowledge receipt of a valid renewal application and shall start the procedure in accordance with the recommended starting dates published on the EMA website." nor does Annex 1 clarify the time needed for the validation. EFPIA proposes to include the days needed by EMA for validation in section 3.2 as well as in Annex 1.	The post-authorisation procedural guidance and the revised SOP will reflect clearly this information.

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73 – 75	7	Comment: From July, the renewal procedure will involve the CHMP Rapporteur and Co-rapporteur as well as the PRAC Rapporteur who have been appointed for that medicinal product. If needed in case of major safety concerns, the PRAC may be consulted. We believe that the PRAC Rapporteur should be appointed for the lifecycle of the marketing authorisation of the product, including all subsequent evaluations as they will have the most expertise on the product.	A systematic involvement of the PRAC Rapporteur is envisaged for all CAPs. The PRAC Rapporteur will also be in charge of drafting the RMP AR in those cases, where a new or updated RMP is submitted. The PRAC Rapporteurship will be described in a separate document, since this is not a procedure specific for Renewals.
74-75	4	Comment: This section states that 'If needed in case of major safety concerns, the PRAC may be consulted' as part of the renewal procedure. Additional clarification around this statement would be helpful given that the PRAC rapporteur and the PRAC will be involved in all renewal procedures as per renewal timetable outlined in Annex I (starting at line no. 380). Proposed change (if any): Please consider adding clarification on whether this would be a separate assessment, at what point in the renewal procedure this assessment would be triggered and what impact it would have on the renewal timetable.	The CHMP is the scientific Committee responsible for adopting an Opinion on the Renewal. The PRAC will provide an assessment report / advice within the timeframes reflected in the Guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 74-75	2	*If needed in case of major safety concerns, the PRAC may be consulted* Comment: What will be the timeline of this consultation? What is the procedure if safety concerns appear during the renewal assessment? Proposed change (if any): NA	See comment above.
78-79	3	Comment: Will the renewal documentation be a modular document as proposed for the PSUR/DSUR? Proposed change (if any):	The revised format as reflected in the Guideline should be followed as of the 2 July 2012.
80, 144 and 468	3	Comment: Given agencies share inspection findings, the need to include these in a renewal application is unclear. Also, between the main text and annexes there is lack of clarity regarding all findings or only those affecting benefit-risk as in lines 144-146. Given that grading of findings relates to risk to public health we recommend aligning with critical or major findings if needed at all. Proposed change (if any):	Comment accepted. The requirement for a summary of all findings is deleted. The guideline text has been reworded to clarify the information required.

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Line 106 - 108	1	Comment: Due to the limited amount of time during the renewal procedure, where the Experts are already asked to work on answers to questions it might not be possible to update the RMP in addition. Furthermore the final renewal assessment might require an additional update of the RMP. Therefore it is proposed to receive the request for an update of the RMP following the renewal procedure. Proposed change (if any): Where such statement is provided, the CHMP may nevertheless consider an update of the RMP necessary and can request its submission ~~during~~ after completion of the renewal procedure.	Not agreed. It is the responsibility of the MAH to assess the need to submit a new or updated RMP as part of the Renewal application in view of the available safety data. Taking into account the extension allowed by the new legislation for the renewal procedure, it is considered that all relevant aspects are to be resolved within the renewal procedure. A clock-stop can be scheduled if further amendments are considered needed.
116	3	Comment: Is it the intention that the addendum to the clinical overview will consist of modules from the PSUR? Proposed change (if any):	The revised format as reflected in the Guideline should be followed as of the 2 July 2012.

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Lines 126-128	1	Comment: In line with our general comment (mix clinical overview and PSUR), EFPIA proposes to modify this paragraph taking into account that off-label use, misuse, or new use are reported in PSURs. *Additional comments for clarification of the text in lines 126-128 are included in section 3. of these EFPIA comments.* Proposed change: The information shall include both positive and negative results of clinical trials and other studies in all approved indications and populations, ~~whether or not included in the marketing authorisation,~~ as well as safety data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.	The text is derived from GVP and it is of relevance to have data in all indications, as the impact of safety issues in unauthorised indication needs to be taken into account for B/R assessment.
131	6	Comment: Specify the statement "clinical expert should be medically qualified". Is a non-medically clinical expert still acceptable, in view of signing off the CO. Proposed change (if any):	The wording has been amended as: "… The clinical expert should have the necessary technical or professional qualifications. And should not necessarily be the same qualified person responsible for pharmacovigilance…"
Lines 143-146	1	Comment : As noted in more detail in the general comments section, EFPIA considers that a "...critical assessment of the impact of the finding on the benefit/risk balance of the medicinal product" is not relevant in the context of the majority of inspections (particularly routine inspections) which are mainly focused on processes and	Comment partly accepted. The requirement is considered relevant as the importance of the findings is not determined by the reason for which the

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		systems rather than products. Where inspections do focus on a particular product, they are generally triggered by benefit risk concerns. EFPIA thus proposes to require an assessment only in case of findings of an inspection which was specifically triggered by a benefit risk concern for the product, or in case of critical or major findings in other inspections which are explicitly considered to have an impact on benefit risk in the final inspection report. Only if a critical assessment is needed based on the above, it should be part of the Addendum to Clinical Overview and discussed in the safety section of this document. The general "History of pharmacovigilance system inspections and summary of the findings" should be included in the Annexes of module 1.2 (as detailed in line 468). In addition, it is not clear whether local inspections should also be included in this assessment. Clarification on these points would be highly welcome. Proposed changes: "...as well as ~~a critical~~ an assessment of ~~the impact of the findings on the benefit/risk balance of the medicinal product~~ whether the pharmacovigilance system is considered to be in general compliance with applicable legislation as a result of the implementation of corrective and preventative actions to inspection findings. If an inspection has been triggered by specific benefit risk concerns for the medicinal product or if critical or major findings specifying an adverse impact on benefit risk of the product concerned have been included in the final inspection report, these findings should be discussed in the assessment.	inspection was initiated (triggered/product specific or routine). In addition, although the critical or major findings revealed during a pharmacovigilance inspection may relate to a deficiency in the pharmacovigilance systems, practices or processes and not be explicitly product specific, a deficient pharmacovigilance system may have an impact on the information available to assessors for the assessment of the benefit/risk balance of the medicinal product. For this reason inspection status should be taken into account during the renewal application. Finally, there is no distinction in the validity/importance of the different types of inspections (supervisory authority, local inspections) and therefore all types of inspections should be listed and taken into account in the impact analysis. The

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			requirement for submission of summary of findings is deleted. The guideline text has been amended to clarify further the submission requirements.
143-146	7	Comment: The scope of the requirement to include a statement on inspection status should be further clarified. Pharmacovigilance systems may operate globally and not all inspections of the PV system or findings will be relevant to the particular product that is the subject of the renewal application. Proposed change (if any): The text should be revised as follows to further clarify the scope of this requirement: "The marketing authorisation holder should provide a history of the relevant pharmacovigilance system inspections conducted by the supervisory authority for centrally authorised products in the EEA during the period covered by the renewal as well as a critical assessment of the impact of ~~the~~ any major or critical findings on the benefit/risk balance of the medicinal product."	See amended text.
144	3	Comment: Provision of inspection findings are reassessed – but this is confusing if an MAH has responded and response accepted by an inspectorate – what is the purpose and likely consequences of reassessment of inspection findings at renewal? Proposed change (if any):	Accepted. Provision of inspection findings will not be required.
194-196	2	*Serious public health concerns should be addressed as part of the renewal*	In line with the European

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		process and the product will not be renewed if serious public health issues remain at the end of the procedure (see also section 3.5.2) or if an existing suspension on the marketing authorisation cannot be lifted. Comment: Could you please clarify what will be the procedure and potential outcome in case of a suspension, which is still under assessment at the time of expiry of the MA, and could possibly be lifted? Proposed change (if any): NA	Commission interpretation, it is confirmed that if at the time of the Renewal, the MAH is not in a position to provide the necessary evidence to allow the lifting of the suspension, the MA will expire.
200-201	2	*At time of renewal, compliance by the MAH with the conditions imposed on the medicinal product will be evaluated. As a result, these conditions could be modified and/or new conditions could be imposed.* Comment: Could you please clarify what would happen for the conditions fulfilled, are they going to be removed? Proposed change (if any): NA	It some/all of the imposed conditions on the MA are assessed and found fulfilled at the time of the Renewal, they will be removed from the MA.
207 210 492	6	Comment: Typo – delete full stop Typo – delete 9 Typo – delete "of location" Proposed change (if any):	Amended.
229	3	Comment: Could there be clarification around the statement that "no new studies are to be submitted within the renewal"? Does this mean that no CSRs may be submitted during the nine months of the renewal, and variations relating to these	The sentence "no new studies are to be submitted within the renewal" refers to the fact that

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		studies must wait until after the renewal is completed? Proposed change (if any):	the MAH should not introduce changes /new studies at renewal and as such substitute to their obligation to keep the MA up to date. With regard to submission in parallel of the renewal, as indicated in the post-authorisation procedural guidance published on the EMA website. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000038.jsp&mid=WC0b01ac058023e7c&jsenabled=true It should be avoided but can be discussed on case by case basis with PTL.
235-237	4	Comment: It is not clear at what stage in the renewal procedure that the applicant receives feedback from the EMA regarding the check performed by EMA, in collaboration with the Member States, on the SmPC, labelling and package leaflet to ensure compliance with the relevant EU legislation and guidance docs. Proposed change (if any): Consider to include this component in the renewal	Any necessary scientific review of the product information will be performed throughout the procedure of the renewal and will be reflected in the assessments from the Rapporteur and the CHMP.

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		timetable. Ideally this feedback should be included in the day 60 assessment report.	In addition a linguistic review of the product information will be performed. Further details can be found in the following document published on the EMA website: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004182.pdf
273-280	7	Comment: If the MAH considers that the marketing authorisation should move from exceptional circumstances to normal circumstances, the MAH should be able to include a statement in the renewal application detailing the fulfilment of the specific obligations and the grounds for converting the MA to normal circumstances. Proposed change (if any): A statement should be added to section 3.5.1.1 to this effect.	The MAH can include its justification in this respect in the Clinical Overview and it will be subject to assessment.

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Lines 305-308	1	Comment: The notion of "normal conditions of use" has been removed in the draft revised guideline to reflect the amendments made to Article 116 of Directive 2001/83 by directive 2010/84. As a consequence legal reasons for refusing the renewal of a MA may include cases where a medicine is harmful or where its benefit/risk balance is not positive outside the normal conditions of use. EFPIA would like to stress that the MAH has limited control over how the medicine is used and that this principle should apply only in cases where no measures can be taken to prevent misuse and abuse. Proposed change: "Reasons for marketing authorisation not being renewed could include for instance the cases where the product proves to be harmful or where its therapeutic efficacy according to the SmPC is lacking, or that the benefit/risk balance is not positive, or where its qualitative and quantitative composition is not as declared. However, in cases where the product proves to be harmful or the benefit/risk balance is not positive due to misuse and/or abuse of the product the possibility of safety measures will be considered before a negative opinion is issued."	In line with the grounds as set out in Art 116 of Directive 2001/83/EC.
Lines 308	1	Comment; The intent of the following statement is unclear: 'Therapeutic efficacy is considered to be lacking when it is established that therapeutic results cannot be obtained with the medicinal product.' EFPIA assumes that the initial granting of the MA has been based on a positive B/R assessment and therefore that the therapeutic efficacy of the product has been established. This statement is unclear and needs to be further clarified or reworded.	In line with the grounds as set out in Art 116 of Directive 2001/83/EC.

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Lines 313-316	1	Comment: It appears unreasonable that a suspended MA must expire if the MAH cannot demonstrate that the benefit-risk balance is positive and cannot identify measure for safe and effective use to allow lifting the suspension. If activities are underway, but not yet completed, to address the concerns that led to the suspension, the MAH should be allowed the opportunity to complete these activities before further action is taken: it would be inconsistent for the Agency to conduct an evaluation of the risk-benefit balance, and then mandate that there must be a different regulatory outcome (i.e. loss of the MA) based on the same data as led to the suspension. Upon generation of data that might have led to lifting of the suspension, the MAH would be obliged to submit a new MA application, if the provisions of this guideline were followed, which would be unnecessarily burdensome on both the MAH and regulators. It should also be noted that Art.14 (2) of the regulation states that the MA may be renewed "on the basis of a re-evaluation by the Agency of the risk-benefit balance": there is no requirement that the benefit-risk balance be positive. Proposed change: Delete lines 313-316.	In line with the European Commission interpretation, it is confirmed that if at the time of the Renewal, the MAH is not in a position to provide the necessary evidence to allow the lifting of the suspension, the MA will expire.

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323, 378	3	Comment: Please clarify in line with EU framework that a public summary of opinion will be publicly available on the Agency portal and that further information on the reasons for a negative opinion will only be made public once the appeals have been held and a final Commission Decision has been adopted? Proposed change (if any):	This statement is in accordance with the current EMA communication policy, which is publicly available. Negative opinions on renewals follow by analogy 'recommendations for the withdrawal/suspension of marketing authorisation'. There will therefore be communication as appropriate (e.g. press releases or Q&As), giving reasons for the opinion at the time of CHMP opinion. Updates are made following re-examination and issuance of an EC decisions. See policy on safety-related communication: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/07/WC500094757.pdf

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325	2	*In case of non-renewal, where applicable an Article 20 or 107i procedure might be initiated*. Comment: Could you please clarify what would be the cases for such an assessment/procedure after a renewal procedure? What would be the added value of a second assessment? Proposed change (if any): NA	It is acknowledged that redundant procedures should be avoided. However, it may not be excluded that a refusal of the renewal requires the trigger of an Art.20 or 107i, taking into consideration the criteria set out for such procedures, in particular when it concerns other medicinal products containing the same active substances.

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Lines 346-354	1	Comment: As the first paragraph refers to submission of example specimens with the renewal application, it seems to be misplaced under a general heading 'Follow-up to the CHMP opinion'. The same applies to specimen submission in Iceland. With the 'Revised Checking Process of Mock-Ups and Specimens' (EMEA/305821/2006), requirements for submission of specimens prior to launch has been reduced to one worst-case specimen per each strength, pharmaceutical form and container type only. The same applies to submission of specimens for renewal products, according to the European Medicines Agency's Post-authorisation procedural advice for users of the centralised procedure (EMEA-H-19984/03 rev 20 Sep 2011). It is unclear why now specimens for all Member States should again be required. Furthermore, Norway has up to now not requested submission of specimens in the context of a renewal. Proposed change : Shift to section 3.3. Documents to submit. In addition there is actually no added value in providing specimens for the renewal of a marketing authorisation, mock-ups should be sufficient. "Mock-ups ~~**and specimens**~~ Where the package leaflet and outer and inner labelling have been amended as a result of the renewal procedure, no mock-ups are required to be provided within the renewal procedure. However, one "worst-case" (multi-lingual pack for e.g. Belgium, Nordic or Baltic countries) ~~specimen~~ mock-up of the currently marketed outer and inner labelling and printed package leaflet for each pharmaceutical form should be provided as part of the renewal application. ~~Revised specimen for all Member States implementing the changes agreed as part of the renewal must be provided to the EMA before launch~~. Revised ~~specimen~~ mock-ups for Iceland ~~and Norway~~ must be provided to the respective authorities directly. "	Wording has been amended for clarification and can be found in Annex 2.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
352 – 354	7	Comment: "Revised specimens for all Member States implementing the changes agreed as part of the renewal must be provided to the EMA before launch. Revised specimens for Iceland and Norway must be provided to the respective authorities directly". This is not in line with the "Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure" which requires only worst-case specimens to be submitted Proposed change (if any): *Remove 352-354. The requirements for worst-case specimens are covered under line 347 – 351.*	Wording has been amended for clarification and can be found in Annex 2.
355-370	7	Comment: The procedure for a re-examination of the Opinion has the potential to take a considerable amount of time. A specific comment should be made in this guideline to allow the maintenance of the Marketing Authorisation beyond the expiry date in the case that a re-examination process is ongoing. Proposed change (if any): Add a statement at the end of this section to reflect this - "At the end of the re-examination procedure, the EMA will publish a 'Summary of Opinion' of the CHMP's final Opinion. <u>The MAH should be permitted to maintain the marketing authorisation beyond the date of expiry where a re-examination procedure is ongoing."</u>	Not agreed. Taking into account the extension allowed by the new legislation for the renewal procedure, it is considered that all relevant aspects are resolved within the renewal procedure.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 398-400 Annex 1	1	Comment: The statement "MAH provides answers to list of outstanding issues to CHMP/PRAC (Co-Rapporteur, CHMP, PRAC members and EMA (no clock stop) or (with clock stop: Day 91)." is not clear. We recommend creating a flow diagram for the 2 scenarios (i.e. with or without a clock-stop). It would be more consistent to clarify the possibility of a clock-stop at Day 90 (when the list of issues is forwarded to the MAH), rather than at Day 100 (when the MAH provides answers to these issues). Proposed change: Day 90: Discussion at CHMP : - If no outstanding issues: adoption of opinion. - If outstanding issues clock-stop may be set up*.*: adoption of List of Outstanding Issues + decision on possible oral explanation by MAH. (* footnote: In case of the outstanding issues a clock-stop may or may not be set up at Day 90, depending on the time left prior to the expiry date of the marketing authorisation.) Day 91 (clock stop) or Day 100 (no clock stop): MAH provides answers to list of outstanding issues to CHMP/PRAC (Co-Rapporteur, CHMP, PRAC members and EMA)	The clock-stop is to take place at Day 90. The need for a clock-stop or not to address any remaining issues is to be defined at Day 90. The wording has been amended to introduce clearer guidance.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 411-415 Annex 1	1	Comment: Clarity is required on why there might be some occasions when a clock stop of 30 days could not be set for a renewal as a result of the time prior to expiry date of the MA being insufficient. If the renewal timetable is based on set submission dates, as detailed in line 64, there should always be enough time for at least a 30 day clock stop for the MAH to respond to outstanding issues. Submission of the renewal application 9 months prior to licence expiry should allow enough time for a 30 day clock stop, in addition to completion of a 120 day (4 month) assessment procedure and a 67 day (2 month) decision-making procedure. Proposed change : "... at an oral explanation. In case of outstanding issues a clock stop will be allowed for, if the renewal was submitted by the recommended submission dates. ~~A clock stop can be set ... .~~ Normally the clock stop will be 30 days."	See amendments in the guideline.
Lines 419-421, Annex 2	1	The first sentence is misleading, as the application is **not** expected to include a consolidated version of the complete dossier. The second sentence, referring to a "tab-separated dossier" concerns paper format applications. The guidance should refer to eCTD. Proposed change: "Renewal applications should be submitted in eCTD format, and include as a minimum the documents listed below: ~~have to contain a consolidated version of the file, containing at least the documents listed below. They should be presented, preferably in a tab-separated dossier and in accordance with the appropriate headings and numbering of the EU-CTD format"~~	The wording has been amended.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
419 - 421	7	Comment: Renewal applications have to contain a consolidated version of the file, containing at least the documents listed below. They should be presented, preferably in a tab-separated dossier and in accordance with the appropriate headings and numbering of the EU-CTD format. Submissions are fully electronic. However, this paragraph does not clearly indicate whether a paper version or an electronic version of the documents is required. Proposed change (if any): Renewal applications have to contain a consolidated version of the file, containing the documents listed below. The documents should be presented <u>electronically</u>, ~~preferably in a tab-separated dossier and~~ in accordance with the appropriate headings and numbering of the EU-CTD format.	The wording has been amended.
Line 424, Annex 2	1	Comment: As Centralised renewals are now submitted in eCTD, a comprehensive table of contents should no longer be required. Proposed change: Remove Module 1.1.	Agreed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
437 - 444	7	Comment: Lists of submissions during the renewal period are requested (variations, USR, as well as commitments). However, such submissions are in included in the eCTD lifecycle. Therefore, it would be appreciated if a waiver could be considered for products for which the whole period covered by the Renewal is included in the products eCTD lifecycle.	Not accepted. A chronological list of all post-authorisation submissions since the granting of the initial MAA or last renewal is considered necessary. Particularly, the fact that the submission is in eCTD does not enable to have a comprehensive list of the submission and dates of approval.
Line 446	5	Comment: The sentence "The marketing authorisation holder will be required to provide written assurance that it will undertake the on-going commitments (Follow-Up measures) within an agreed time frame." is no longer present in the draft guideline as it is in in section 3.4 of the current guideline (EMEA/CHMP/2990/00 rev.3). In section 3.5.1.2 of the new draft guideline, the specific obligations have to be outlined in Annex II of the Commission Decision whereas in the current guideline an additional Letter of Undertaking is required. Other post-authorisation measures should be listed in Annex II, as additional pharmacovigilance activities in the RMP or as recommendations included in the CHMP assessment report. This indicates that a Letter of Undertaking is no longer required. However, in section Annex 2 line 446 the Letter of Undertaking is still listed as required. Proposed change (if any): The "Letter of Undertaking" should be deleted from line 446, if applicable	Agreed. In line with EMA procedural announcement, Letters of Undertaking should no longer be submitted. Wording has been amended.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 471-473 Annex 2	1	Comment: While regulatory procedures are aiming at electronic submissions, it is unclear why the product information literature should now always be provided as a paper copy. Would this requirement be applicable only to the initial submission? Furthermore, it is suggested to clarify whether the highlighted version of the proposed text needs to be in the eCTD. TIGes Harmonised eCTD guidance version 2.0 of August 2011 Section 3.2.5 reads *"Product information should be supplied as PDF files but some NCAs require an RTF or Word file in addition to facilitate assessment. Those additional files should be provided in the separate folder XXXX-working documents on the same CD / DVD. [...] It is not required to provide the tracked changes version in PDF format, if it is submitted as Word document in the working documents folder."* We propose to revise to clearly indicate which versions (clean and/or highlighted) need to be in the eCTD and which need to be provided in addition electronically as working documents, taking into account previous process improvements on these aspects. Proposed change: ~~A relevant example of the proposed texts for SmPC, Annex II, outer and inner labelling and Package Leaflet in English has to be provided in paper (highlighted). A full set of Annexes in English should be provided electronically (highlighted).~~The proposed texts for SmPC, Annex II, outer and inner labelling and Package Leaflet should be provided in English in the eCTD, with a highlighted (track changes) copy in MS Word format in the working-documents folder outside of eCTD.	Agree. Text harmonised in the guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
471- 473	7	Comment: A request for paper proposed Product Information is included. However, this is no longer applicable as submissions are fully electronic. All annexes are provided electronically. Proposed change: ~~A relevant example of the proposed texts for SmPC, Annex II, outer and inner labelling and Package Leaflet in English has to be provided in paper (highlighted).~~ A full set of Annexes in English should be provided electronically (highlighted).	Agree. Text harmonised in the guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
492-493	3	Comment: Reference to the master file and number assumes this guidance will come into effect post July 2012 but there will be transitional arrangements for MAHs moving from a DDPS to PVMF that this does not take into account. Proposed change (if any):	The transition to the new PSMF should be done at the time of the Renewal or before July 2015, whichever is the earliest. For renewals submitted as of 2 July 2012 and before July 2015 there is an obligation for the MAH to move to the Pharmacovigilance System Master File (PSMF). The transitional arrangements with the transitional period only apply to the format of the PSMF but not to the requirement to move to the PSMF.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 511-514 Annex 2	1	Comment: The draft guideline indicates that the Addendum to the Quality Overall Summary should include (amongst others): • Currently authorised specifications for the active substance and the finished product • Qualitative and quantitative composition in terms of the active substance(s) and the excipient(s) This information should already be available in module 3 of the eCTD. To avoid repetition we therefore recommend that this information is not reproduced in the Addendum to the Quality Overall Summary. Proposed change (if any): • Reference/link to module 3 of the eCTD with information on the currently authorised specifications for the active substance and the finished product (with date of latest approval and procedure number) • Reference/link to module 3 of the eCTD with information on the Qualitative and quantitative composition in terms of the active substance(s) and the excipient(s)(with date of latest approval and procedure number)	Not agreed.
515-524 Annex 2	1	Comment: Information to be covered in the Non-clinical expert statement should be clarified. Furthermore is our understanding correct that if there is no new non-clinical data, also no non-clinical expert statement is required? In addition, clarification is needed whether the Non-clinical Expert statement can be included in the Addendum to the Non-clinical Overview or should two documents be prepared	An Addendum to the Non-Clinical Overview (including the Non-Clinical Expert Statement) is not required in the case no new non-clinical data have been gathered since the initial MAA or last renewal.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 525-575 Annex 2	1	Comment: The amount of information required seems excessive for a clinical overview addendum which, according to lines 117-125, should consist of a critical discussion of the benefit/risk balance of the product, taking into account the submitted PSURs and additional data. Transitional arrangements are requested by EFPIA for implementation of the changes according to Module VII of the GVP Guidelines: It is proposed that the new PSUR format applies to all reports whose data lock points occur after January 2013. This equates to a 6 month transitional period and has the advantage that it should coincide with Step 4 of ICH E2C (R2) and facilitate international harmonisation. EPFIA therefore requests that the new format of the Clinical Overview, or the ability to refer to a PSUR containing the information requested to be included in the Overview, should be subject to the same transitional period. Also, the reference provided in lines 574-575 to the GVP module on PSURs may be interpreted as if the clinical overview addendum should be in fact a PSUR. It is not clear why it should no longer be possible to submit a PSUR according to the new guidance in parallel to the required confirmatory statements from the Clinical Expert in the Clinical Overview. PSURS are written for global use, therefore the change in approach requested will increase the administrative burden to the applicant and lead to a new type of Clinical overview compared to those documents submitted for marketing authorisation application and/or variations. Clarification is requested on whether the Clinical Expert Statement is a stand-alone document or a conclusion of the Addendum to clinical overview. If it is a stand-alone document, the location in the eCTD should be clearly specified. Proposed change : The reference to GVP module on PSURs should be reworded in order to clarify	The Renewal is a crucial point in the life-cycle of a product, where a re-evaluation of the benefit/risk of the product is performed. PSURs are no longer required as part of the Renewal application. However, a critical discussion on the benefit/risk of the product is needed and consequently it should be provided in the Addendum to the Clinical Overview. The revised Guideline should be followed for renewal submitted as of the 2 July 2012.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		that the clinical overview addendum should be a concise critical review based on the submitted PSURs and on safety & efficacy data generated since the latest PSUR. If the new format of the CO for this purpose is intended to be maintained, then Line 530 should be amended as follows: "The Addendum to the Clinical Overview should contain the following information or should refer to a PSUR containing the following information**:..."	
525 - 575	7	Comment: The EMA appears to be requesting a PSUR in the format of an EU Clinical Overview. The rationale for this change is unclear and it will create practical issues for applicants. In particular, since PSURs are global documents, the proposed change will increase the administrative burden on the applicant as it will require a new type of EU-specific Clinical Overview. Therefore this creates a new requirement as the document is over and above the documents that are submitted for marketing authorisation applications and/or variations. It is unclear why it should no longer be possible to submit a PSUR according to new guidance in parallel to the required confirmatory statements from the Clinical Expert in the Clinical Overview. Proposed change (if any): Amend Line 530 as follows: 'The Addendum to the Clinical Overview should contain the following information or should refer to a PSUR containing the following information**:'	The Renewal is a crucial point in the life-cycle of a product, where a re-evaluation of the benefit/risk of the product is performed. PSURs are no longer required as part of the Renewal application. However, a critical discussion on the benefit/risk of the product is needed and consequently it should be provided in the Addendum to the Clinical Overview. The revised Guideline should be followed for renewal submitted as of the 2 July 2012.
526-529	6	Comment: Qualify the statement "reference to relevant new information in the public	Comment acknowledged.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		domain". Proposed change (if any): Add "considered important and justified to be added by the MAH".	
533 543 552 561 567 570	2	*90 days prior to renewal submission.* Comment: Does this mean that the DLP will be 90 days prior to the submission, rather than 60 days as before? Proposed change (if any): NA	This is in accordance with the new rules for PSUR submissions.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 539-543 Annex 2 (CCSI)	1	Comment: Up to now, a Reference Safety Information was not attached to a Clinical Overview. If submission of a Company Core Safety Information (CCSI) is now requested, it should be taken into account that there is no requirement for companies to create such a specific document. While many EFPIA member companies define the CCSI as part of a Company Core Date Sheet (CCDS), these documents are not always explicitly created. Some companies also use other types of documents (e.g. an SmPC) as their Reference Safety Information. The requirement to submit a track changes version of the document identifying the changes made to the Company Core Safety Information (CCSI) during the period covered since the initial marketing authorisation or since the last renewal appears unnecessarily burdensome as all these will have been reviewed previously in PSURs and in the case of the labelling changes submitted in Centralised variation procedures. Thus, EFPIA proposes to delete the last sentence in this paragraph. Proposed change (if any): 'Significant changes made to the ~~Company Core Safety Information (CCSI)~~ Reference Safety Information (RSI) during the period covered since the initial marketing authorisation or since the last renewal. ~~A track changes version ...”~~	Agreed, this is in line with GVP text.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 544-546 Annex 2	1	Comment: Comparison of the SmPC with the RSI in the body of the Clinical Overview will limit its usability for renewal purposes in other countries/regions. If such comparison is required, we propose it be located in an Annex. Furthermore, the proposed SmPC, Package Leaflet and labelling is already provided in Module 1.3.1 of the dossier. Thus, it seems unnecessary to attach the documents again here. Proposed change (if any): Preferred option is to delete Lines 544-546. If this is not considered acceptable, please change as shown: 'Meaningful differences between the ~~CCSI~~ RSI and the proposals for the Summary of Product Characteristics should be provided in an Annex to the document. ~~A proposed SmPC, Package leaflet and Labelling should also be provided~~'	See above.
549-550	7	Comment: "Data in summary tabulations: cumulative summary tabulation of serious events from clinical trials as well as cumulative summary tabulations of adverse reactions from spontaneous data sources..." The current text excludes data of serious adverse events from non-interventional studies. Proposed change: Data in summary tabulations: cumulative summary tabulation of serious events from clinical trials **and non-interventional studies** as well as cumulative summary tabulations of adverse reactions from spontaneous data sources...	Aligned with the GVP module.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 577-579 Annex 2	1	Comment: Annex 2 is missing the requirement detailed in lines 180-181 that, if no non-clinical data has been gathered since the initial MAA or last renewal, this may be stated in the Addendum to the Clinical Overview, rather than providing a separate addendum to the Non-Clinical Overview. Proposed change (if any): Confirm that no new **non-clinical or** clinical data are available which change or results in a new risk benefit evaluation.	This information is clarified in lines 514-523.

3. Comments for clarification (proposed editorial changes)

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 18	1	Comment: The draft guidance indicates specifically that MAs approved under conditional circumstances are out of scope of his guideline. However, approvals under exceptional circumstances are not mentioned. EFPIA suggests including a statement clarifying that the guideline also applies to MAs approved under exceptional circumstances.	The wording has been amended to introduce this clarification.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 31-33	1	Comment: It is unclear why particular reference is made here to the labelling and package leaflet, but not to other conditions listed in the respective Article of the Regulation, which could lead to a refusal of the authorisation. As Lines 235-237 address the responsibility of EMA, in collaboration with the Member States, to 'check that the SmPC, labelling and package leaflet conform to the requirements of Directive 2011/83/EC and Regulation (EC) No 726/2004 as well as to the relevant Commission and CHMP/EMA guidelines', mention of part of this statement under 'Legal Framework' seems unnecessary. Lines 31-33 are probably included because the following paragraph refers to changes to the labelling and package leaflet being permitted at renewal. If lines 31-33 and 34-39 were included in a single paragraph, it would read more easily. Moreover, use of the official terminology is suggested, as 'patient information leaflet' is not defined in the Regulation (EC) No 726/2004. Proposed change (if any): Include lines 31-33 and 34-39 in a single paragraph and change to "Article 12(1) of Regulation (EC) No 726/2004, indicates that an authorisation shall notably be refused where the labelling and ~~patient information~~ package leaflet do not comply with the requirements of Title V of Directive 2001/83/EC.	The wording has been amended.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 91	1	Proposed change/minor suggestion for clarification: "If a revised Summary of Product Characteristics (SmPC), labelling and/or Package Leaflet (PL) is proposed to take account of issues raised by the author of the applicant's clinical expert statement, the precise present and proposed wording should be specified on the form. Alternatively, such a listing may be provided as a separate document attached to the application form under a tabular format (indicating the current and proposed texts). For minor linguistic or QRD changes, the revisions may be highlighted in track changes in the Annexes only. In such cases a general statement referring to the Annexes in the "proposed product information text" section of the application form should be included. Any other changes not listed, will not be considered as part of the renewal application."	Not agreed. It is always requested for all changes proposed, whether minor or not to be listed, as for all other types of applications. Also, I would propose to say proposed by MAH. See guideline.
Line 95-96	1	Comment: To be consistent with Lines 59-60 (if it remains as it is) and to clarify possible participation of the Rapporteur in pre-submission meetings, a slight amendment is proposed. Proposed change: "In general, proposed amendments to the SmPC should be brought to the attention of the EMA, (and Rapporteur if needed) before submission, preferably through a pre-renewal submission meeting (see also section 3.1)."	Not agreed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 113-114	1	Comment: To be in accordance with Line 499, a slight amendment is proposed. Proposed change: For medicinal products which do not have a Risk Management Plan (RMP), the MAH should state ~~it~~ in Module 1.8.2. that no RMP has been submitted for the concerned product.	See amendments in the guideline.
Line 115	1	Comment: EFPIA suggests to present the different overviews in the order of eCTD Module 2. Proposed change: 3.~~Addendum to Clinical Overview / Quality Overall Summary / Non-clinical Overview~~ Quality Overall Summary / Non-clinical Overview / Addendum to Clinical Overview	Agreed.
Line 116	1	Comment: Please clarify that the Addendum Clinical Overview is an addendum to the Clinical Overview of the initial application or to the last renewal.	The wording has been amended to introduce this clarification.
Line 120-122	1	Comment: A RMP has not been approved for all products, and thus effectiveness of risk minimization measures can only be discussed if a RMP is available. Proposed change:"... taking into account Periodic Safety Update Reports (PSURs) submitted, suspected adverse reactions reports, additional pharmacovigilance activities and the effectiveness of risk minimisation measures contained in the RMP (if available)."	Comment accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 126 – 128 / Annex 2	1	Comment: The draft guidance states that for the clinical overview "The information shall include both positive and negative results of clinical trials and other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation." However, this is not mentioned in section 2.5 of Annex 2 describing the information to be included in the clinical overview. For consistency reasons, EFPIA proposes to either delete above paragraph in line 126 – 128 or add a comment to the same effect in the Annex.	Annex 2 and text in the document have been aligned.
Lines 126-128	1	Comment: It should be clarified that these lines refer to a request for data accumulated since the initial MAA or the last renewal, as per lines 119-122. Proposed change: "The new information referred to above shall include both positive and negative results ... "	Agreed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 468	1	Comment: It is proposed to update line 468 to specify the time frame to be covered and add the information regarding necessity of a critical assessment (see comment on lines 143-146). Proposed change: Add "... summary of the findings during the period covered by the renewal. If a critical assessment of the impact of the findings on the benefit/risk balance of the medicinal product is required, it should be included in the Addendum to Clinical Overview."	Comment is acknowledged.
Lines 169-170	1	"…a list of the most recent GMP inspections carried out indicating the date, inspection team and outcome should be provided." The term "most recent" is not clear in conjunctions to the inspection**s** (plural) and should be clarified in that only the most recent inspection for each site has to be listed. Otherwise the sentence could be misread as requiring a list of all inspections from the initial MAA until renewal. Proposed change: "…a list of the most recent GMP inspection carried out at each site indicating the date, inspection team and outcome should be provided."	Not accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 202-205	1	Comment: For a better understanding, EFPIA proposes to clarify the entities providing the relevant assessments and recommendations which need to be taken into account for updating the product information. Proposed change: "... the product information is up to date with the current scientific knowledge including the conclusions of the assessments and recommendations <u>from the PRAC as well as CHMP opinions</u> made publicly available on the European medicines web-portal."	No amendment to the wording which is as set out in Article 16(3) of Regulation (EC) No 726/2004.
445-446	1	Comment: As per our understanding the "signed letter of under taking" is no longer required to be submitted as part of the CP renewal application. If our understanding is correct the wording could be modified as indicated below. Proposed change (if any): • Revised list of all remaining conditions and Specific Obligations ~~and signed Letter of Undertaking (where applicable)~~	Wording has been amended.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
line 474 (Annex 1)	1	Comment: Editorial change in line with our comment on lines 346-354 Proposed change: 1.3.3 ~~specimen~~ Mock-ups One "worst-case" (multi-lingual pack for e.g. Belgium, Nordic or Baltic countries) mock-up of the currently marketed outer and inner labelling and printed package leaflet for each pharmaceutical form should be provided.	Wording has been amended for clarification and can be found in Annex 2.