18 July 2016
EMA/723788/2015
Committee for Medicinal Products for Human Use

Overview of comments received on 'Guideline on the processing of renewals in the centralised procedure – EMEA/CHMP/2990/00 Rev. 5'

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

Stakeholder no.	Name of organisation or individual
1	EFPIA – Pär Tellner par.tellner@efpia.eu
2	EGA (European Generic and Biosimilar medicines Association) Contact person: Beata Stepniewska, Deputy Director General, Head of Regulatory Affairs EGA; beata@egagenerics.com
3	Dr Aurélie Mahalatchimy and Prof Alex Faulkner on behalf of the REGenableMED consortium aurelie.mahalatchimy@gmail.com
4	Teva Pharmaceuticals Europe, Dr Leda Pittarello, Principal Regulatory Affairs Officer, Leda.Pittarello@tevaeu.com

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**CMDh alignment** The changes in content of the documentation required for renewal for a Centralised Product, for example with respect to the Addendum to Clinical Overview, should also be reflected in the CMDh Best Practice Guide on the processing of renewals in the MRP/DCP procedure (CMDh/004/2015/Rev 12). It is believed that a closer alignment between the two guidance documents will facilitate the development of MAH's standard templates independently from the renewal procedure.	The Agency has considered the proposal for the submission requirements for products authorised under article 10(1) and 10a of Directive 2001/83/EC and for which PSUR submission is not required, in line with the pilot initiated by the CMDh for products authorised through the MRP/DCP. In view of: - the new renewal process recently implemented within the EMA and designed to streamline and facilitate the renewal procedures for centrally authorised products - the CMDh pilot has been recently implemented and further feedback on the efficiency gained is awaited This proposal would not be implemented at this stage but will be considered by the Agency at a later stage.
1	**Advanced Therapies Medicinal Products** The guidance does not cover the case of ATMPs, in particular it does not describe how the CAT may be involved.	Change agreed. A general reference to the involvement of the CAT for ATMP has been included in the guideline. Further details on the interactions, the roles and responsibilities of the CAT are provided in the "*Procedural advice on the evaluation of advanced therapy medicinal product in accordance with article 8 of Regulation (EC) no 1394/2007*" published on the EMA website.
1	**Scientific Advisory Groups** The role of the Scientific Advisory Groups is to 'provide an independent recommendation on scientific/technical matters related to products under evaluation through centralised regulatory procedures and Referrals by the CHMP or any other scientific issue relevant to the work of the Committee'. It would be helpful to understand whether this expertise can also be	A SAG could be convened at the request of the CHMP during a renewal procedure in the cases where the need to consult on scientific questions is raised, in line with the mandate and objectives of the SAG: "*The SAG is established to provide an independent recommendation on scientific/ technical matters related to products under evaluation*

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	called upon by the CHMP in the context of a renewal, when diverging views/split opinions within the CHMP occur. Reference: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/06/WC500091622.pdf	*through centralised regulatory procedures and Referrals by the CHMP or any other scientific issue relevant to the work of the Committee."*
1	**Benefit-risk methodologies** The assessment process described in the guidance does not seem to take into account new methodologies that are now used for new initial authorisations. It is important that that there is a consistency on the methodologies used to measure, and to report, benefit and risk throughout the lifecycle of the product, and it is unclear how this will be done. In particular, it is unclear how CHMP will e.g. re-assess during the renewal the uncertainty in the knowledge about the beneficial/unfavourable effects, or update the effects tables if these have been prepared at the time of initial authorisation.	Methodologies applied for initial marketing authorisation applications are also valid for renewals. As such the guidance on the assessment of uncertainty in the knowledge about the beneficial /unfavourable effects applies also for the renewal procedures.
	Variations during the renewal procedure It is clear from the guidance that no new studies should be submitted with the renewal unless they impact the benefit-risk balance. Furthermore, the guideline makes it clear on lines 257-259 that MAHs must refrain from submitting substantial changes within the renewal procedure. However, it is not clear to what extend MAHs can submit variations during the 9-month time-window of the renewal procedure. While EMA generally advises that variations should be avoided while the renewal is on-going, for very active products, it is unlikely that no variation will be needed during this time-period. In order to facilitate the overall planning for MAHs, guidance on which type of variations may or may not be submitted as separate / standalone procedures during the renewal procedure time-window, and under which criteria, would be helpful and would ensure operational efficiencies. It would also be useful to have the opportunity to discuss this in a pre-submission meeting.	Details on procedural aspects for handling of variation applications during the renewal procedure have been included in the Questions and Answers related to Renewals and published on the EMA website (see question 8 *How to handle other ongoing variation applications during the renewal procedure and what impact may ongoing procedures have on the renewal procedure?*). The guideline mentions that the "*MAH can contact the procedure manager at the EMA responsible for the product. Exceptionally, if necessary and further to the consultation with the EMA, a pre-renewal submission meeting can be organised in advance in a date compatible with the renewal submission*."
1	*Editorial comment* There are inconsistencies in the document regarding the expression 'benefit-risk balance', which is sometimes expressed as benefit/risk balance, benefit-risk ratio, or risk-benefit balance, etc. In line with	Change agreed. The reference to the benefit-risk balance has been harmonised through the document using "**benefit-risk-balance**".

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	the EMA website, it is recommended that '**benefit-risk balance'** is used consistently throughout the document.	
2	EGA and EBG, its sector group representing biosimilar medicines, welcomes the further development of the "Guideline on the processing of renewals in the centralised procedure". EGA highly appreciates EMA's efforts to continuously improve guidance documents taking authority's and industry's experiences into account, as well as the needs and challenges faced by the industry. Thereby EMA facilitates the availability of clear, up-to-date guidance documents, and consequently, the daily regulatory work on both sides. The inclusion of new information related to the role of PRAC/PRAC Rapporteur, the addition of references to specific query groups and more specific advices on Addendum to clinical overview make the guidance very transparent. As the EGA members are users of both, the CP and the DCP procedures, detailed recommendations made in the next section are driven by the EGA members' wish to have a harmonized approach to the renewal process across all types of procedure. In the draft guideline additional data/information is required in the M2.5 Addendum Clinical Overview for CP renewals, resulting in different requirements compared to MRP/DCP renewals. The EGA would like to have the data requirements harmonized for all types of procedure, so companies can cover multiple renewals with the same Addendum Clinical Overview, regardless of type of procedure used. As of 1st of January 2015, it is acceptable for MRP/DCP renewals to submit in the renewal package a Clinical Expert Statement only,	The Agency has considered the proposal for the submission requirements for products authorised under article 10(1) and 10a of Directive 2001/83/EC and for which PSUR submission is not required, in line with the pilot initiated by the CMDh for products authorised through the MRP/DCP. In view of: - the new renewal process recently implemented within the EMA and designed to streamline and facilitate the renewal procedures for centrally authorised products - the CMDh pilot has been recently implemented and further feedback on the efficiency gained is awaited This proposal would not be implemented at this stage but will be considered by the Agency at a later stage.

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	instead of a full Addendum Clinical Overview, for products falling under the art. 10(1) and 10a of Directive 2001/83 and for which according to the EURD list a PSUR is no longer required. In the CP guideline, there is no mention on the 'waiver' for products for which no PSURs are required. We would welcome the option to omit certain elements of the Addendum Clinical Overview for art. 10(1) and 10a products for which PSUR submission is not required according to EURD list in line with the MRP/ DCP as the same objective and principles of renewal applies to certain types of products (irrespective of their MA routes). Please find below the EGA proposals to amend the guideline which reflects the general comment raised above.	
3	All the partners of the REGenableMED project are aware of the existence of this draft Guideline. We welcome the opportunity to review this Guideline on the processing of renewals in the centralised procedure.	
3	A list of abbreviations used in this guideline should be provided at the end of the document to facilitate its understanding and as it is generally done in the EMA's guidelines.	
4	Can the content of the Addendum Clinical Overview (data to be included in the Addendum Clinical Overview) be harmonized with the requirements as set forth in the MRP/DCP renewal guideline, because generic companies often cover multiple renewals with the same Addendum Clinical Overview, so we prefer to have harmonized requirements on the content, not different data requirements related to procedure type (CPs versus MRP/DCP).	
4	Can the EMA add in the revised CP renewals guideline the option to	The Agency has considered the proposal for the submission

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	omit certain elements of the Addendum Clinical Overview for art. 10(1) and 10a products for which PSUR submission is not required according to EURD list (same principle as for MRP/DCP renewals)?	requirements for products authorised under article 10(1) and 10a of Directive 2001/83/EC and for which PSUR submission is not required, in line with the pilot initiated by the CMDh for products authorised through the MRP/DCP. In view of: - the new renewal process recently implemented within the EMA and designed to streamline and facilitate the renewal procedures for centrally authorised products - the CMDh pilot has been recently implemented and further feedback on the efficiency gained is awaited This proposal would not be implemented at this stage but will be considered by the Agency at a later stage.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
39-50	2	Comment: We would welcome the option to omit certain elements of the Addendum Clinical Overview for art. 10(1) and 10a products for which PSUR submission is not required according to EURD list (same principle as for MRP/DCP renewals as explained in general comments). Proposed change (if any): Add: "For renewal applications submitted from <date>, certain elements of the clinical overview addendum can be omitted for products authorised under Articles 10(1) and 10a of Directive 2001/83/EC, unless there is an obligation to submit PSURs for the product as laid down in a condition to the Marketing Authorisation or it is indicated in the list of European Union Reference Dates (EURD) that PSURs are required for products authorised or registered under these articles and containing the substance or combination of substances concerned."	The Agency has considered the proposal for the submission requirements for products authorised under article 10(1) and 10a of Directive 2001/83/EC and for which PSUR submission is not required, in line with the pilot initiated by the CMDh for products authorised through the MRP/DCP. In view of: - the new renewal process recently implemented within the EMA and designed to streamline and facilitate the renewal procedures for centrally authorised products - the CMDh pilot has been recently implemented and further feedback on the efficiency gained is awaited This proposal would not be implemented at this stage but will be considered by the Agency at a later stage.
52-53	1	**Comment:**	Change agreed. The following statement was

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		The validity of a centralised MA is linked to the date of notification of the MAH, as reported in the EU OJ, from which the date of the renewal(s) will be calculated. This needs to be reflected in the guidance. **Proposed change:** In accordance with Article 14(1-3) of Regulation (EC) No. 726/2004, a marketing authorisation (MA) is valid for five years from the date of notification of the Commission Decision to the MAH, except when a "conditional marketing authorisation"[2] has been granted.	included in the guideline: "*The 5-years period will be counted from the date of notification of the Commission Decision to the MAH"*
86-88	1	**Comment:** Please provide advice on how the renewal Data Lock Point should be set with regards to the proposed submission date. Guidance should be provided on the possibility to use the same DLP as the PSUR and the documentation to be provided should the renewal DLP and PSUR DLP be different.	The DLP for the renewal submission usually would not coincide with the DLP of the PSUR. The following sentence is included in the guideline to clarify this question: *"The discussion should also clearly reflect the data included in the previous PSURs and the new data that have been collected since the DLP of the last PSUR up to the DLP of the renewal that should not exceed 90 days prior to the submission of the renewal application".*
92-94	1	**Comment**: Please clarify timelines, process and format for applying for a renewal pre-submission meeting as this is currently not included in any guidance.	Experience shows that queries are successfully addressed via email. Therefore, applicants are encouraged to firstly raise the questions related to the renewal to the EMA via email. Based on the questions received the procedure manager will discuss with the applicant the best way to address them, including the potential need for a pre-

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			submission meeting. The document was revised to include "*Exceptionally, if considered necessary by the MAH and further to the confirmation with the EMA, a pre-renewal submission meeting can be organised in advance in a date compatible with the renewal submission.*"
115 and 116	1	**Comment:** The application form of the renewals is available under (Volume 2B and not Volume 2C) in the Notice to applicants. **Proposed change:** "The renewal application form should be completed. The form is available in the Notice to applicants (Volume 2B[7]).”	Change agreed.
115-116	1	**Comment:** The guidance does not acknowledge that the use of the electronic renewal application form has now been mandated for the centralised procedure. Consider changing footnote 7 to link not to the NTA but to the eAF eSubmission website http://esubmission.ema.europa.eu/eaf/index.html **Proposed change:** The renewal application form should be completed electronically. The electronic EU renewal application form is available from the eSubmission website ~~in the Notice to applicants (Volume 2C[7])~~.	Change agreed.
117-120	1	**Comment 1:** Define what is meant by the 'core EU number'.	Changes agreed.

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		Comment 2: A MAH may decide NOT to renew one or more presentation(s) of the product. This may be done by indicating it on the cover letter, but it should also involve removing the presentations from the table. **Proposed change:** The marketing authorisation holder should complete one renewal application form for the Centrally Authorised Medicinal Product (= 1 application per ~~core~~ MA EU Number, appending a list of all authorised strengths, pharmaceutical forms and presentations of the product concerned for which renewal is sought. In cases where the MAH does not wish to renew certain product presentations (e.g. a certain pharmaceutical form, strength or pack-size), this should be clearly indicated in the cover letter and these should not be included in the appended list**.**	
121-122	1	**Comment:** Apart from a revised Summary of Product Characteristics (SmPC), labelling and/or Package Leaflet (PL) that is proposed to take account of issues raised by the expert, also other issues may impact on the product information and should be considered within the renewal procedure, like changes due to the revision of the SmPC guideline, other relevant guidelines impacting on the product information, or EMA/QRD Product Information Templates. • While this is acknowledged in the section 3.4 Assessment process (lines 247-250), guidance should also be provided here on whether the Product Characteristics, labelling and/or Package leaflet should be updated in line with the latest guidance impacting the PI.	Change agreed.

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		• In all of these cases the section "present/proposed" in the application form should clearly list all changes introduced to the product information (incl. any minor linguistic amendment introduced for each language). **Proposed change (if any):** If a revised Summary of Product Characteristics (SmPC), labelling and/or Package Leaflet (PL) is proposed within the renewal procedure ~~to take account of issues raised by the expert~~, the precise present and proposed wording should be specified on the form.	
122	3	A list of abbreviations used in this guideline should be provided at the end of the document to facilitate its understanding and as it is generally done in the EMA's guidelines.	Change agreed
129-132	1	**Comment:** According to Annex 2, the compliance declaration should be provided separately in tabular format as part of the Quality Expert Statement in the 2.3 Addendum to Quality Overall Summary (see lines 508-520) for centrally authorised products (CAPs). To prevent confusion for renewal applications for CAPs revised text is proposed. **Proposed change (if any):** The 2.3 Addendum to Quality Overall Summary also incorporates a declaration to be signed stating that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress, and that the product conforms with current CHMP quality guidelines, where relevant.	A reference to the annex 2 Documents to submit: 2.3 Addendum to Quality Overall Summary has been included in the document

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162	1	**Comment:** Additional text added to the end of the sentence to reflect current practice. **Proposed change (if any):** …should also be included in tabular format. Alternatively there is no need to provide the tables if active hyperlinks are available in the addendum to the quality overall summary. Dates of the latest approval and procedure number are required to be provided.	Change agreed.
127	1	**Comment:** Propose to add the email address of the query service (Renewalquery@ema.europa.eu). **Proposed change (if any):** "…submission, preferably via the query service (Renewalquery@ema.europa.eu) or during a pre-renewal submission meeting when…"	Not applicable. It was replaced by the "procedure manager responsible for the product"
139	1	**Comment:** Propose to add the PRAC in the decision to update the RMP. **Proposed change:** "…Addendum to the clinical overview. Where such statement is provided, the CHMP and the PRAC may nevertheless…"	Change agreed.
181	1	*Editorial comment* **Comment:** Amended text within the sentence **Proposed change (if any):** In the case no new non-clinical data have been gathered	Change agreed

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		since the granting of the initial MA or last renewal, this may	
181	1	*Editorial comment* **Proposed change**: In the case no new non-clinical data have been ~~gathered~~ generated since the initial MAA or last renewal or there is no new relevant information in the public domain, this may be stated in the Addendum to the Clinical Overview.	Change agreed.
190-221	2	Comment: We would welcome the option to omit certain elements of the Addendum Clinical Overview for art. 10(1) and 10a products for which PSUR submission is not required according to EURD list (same principle as for MRP/DCP renewals) Proposed change (if any): Add after line 205: "Some information can be omitted from the addendum to the clinical overview for products authorised under Articles 10(1) and 10a, unless there is an obligation to submit PSURs for the product as laid down in a condition to the MA or it is indicated in the list of European Union Reference Dates (EURD) that PSURs are required for products authorised or registered under these articles and containing the substance or combination of substances concerned. It should be noted that where PSURs are not required to be submitted, the MAH is still obliged to monitor the safety of the product, detect signals, evaluate these, and if necessary submit updates	The Agency has considered the proposal for the submission requirements for products authorised under article 10(1) and 10a of Directive 2001/83/EC and for which PSUR submission is not required, in line with the pilot initiated by the CMDh for products authorised through the MRP/DCP. In view of: - the new renewal process recently implemented within the EMA and designed to streamline and facilitate the renewal procedures for centrally authorised products - the CMDh pilot has been recently implemented and further feedback on the efficiency gained is awaited This proposal would not be implemented at this stage but will be considered by the Agency at a later stage.

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		through the appropriate regulatory procedure."	
193	1	*Editorial comment* **Comment:** Amended text within the sentence **Proposed change (if any):** Product on the basis of a consolidated version of safety/efficacy data accumulated since the granting of the initial MA ….	Change agreed.
194, 198,225,440,532, 533,535,536,551, 554,555,571,581, 603	1	**Comment:** Propose to change through the texts: the Periodic Safety Update Reports (PSURs) by Periodic Safety Update Reports (PSURs)/Periodic Benefit Risk Evaluation Report (PBRER) **Proposed change:** "…or the last renewal, taking into account Periodic Safety Update Reports (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) submitted, suspected…."	PSUR terminology is now only used in the guideline
239	3	Comment: The CAT should also be involved for an Advanced Therapy Medicinal Product. Proposed change (if any): The renewal procedure will involve the CHMP and the PRAC as well as the CAT when the medicinal product is an Advanced Therapy Medicinal Product.	Change agreed.
240-241	1	**Comment**: The CHMP's recommendation for one additional five-year renewal in based on criteria relating to pharmacovigilance. These are further defined in the context	Change agreed. The following statement was included: "*The grounds on which the CHMP may decide to*

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		of Directive 2001/83/EC Article 24(3) as '*justified grounds relating to pharmacovigilance, including for example exposure of an insufficient number of patients to the medicinal product'*. It would be useful to have these criteria listed as well so that consistency is ensured with products authorised under the Directive, and that it is clearer for MAHs when a further renewal will be required. **Proposed change**: On the basis of the overall re-evaluation of the benefit-risk balance, the CHMP may recommend to grant unlimited validity to the Marketing Authorisation, or to require one additional five-year renewal. The grounds on which the CHMP may decide on an additional renewal will be duly justified and relate to pharmacovigilance, including for example exposure of an insufficient number of patients to the medicinal product.	*require an additional renewal will be duly justified and relate to pharmacovigilance, including for example exposure of an insufficient number of patients to the medicinal product. Criteria considered by CHMP are set out in the CHMP "Reflection Paper Criteria for requiring one additional five-year renewal for Centrally Authorised Medicinal Products*".
249-250	1	**Comment**: Updates of the PI are not always necessary. **Proposed change**: If necessary**,** proposed changes to the SmPC, labelling and PL must be indicated on the renewal application form.	Change agreed. The following statement was included: "*changes are necessary to the SmPC, labelling and PL, **as appropriate,** arising from the renewal evaluation,*"
268	1	*Editorial comment* **Comment:** Typo in sentence. **Proposed change:** "Regulation (EC) No 726/2004 as well as ~~of~~ to the relevant Commission and CHMP/EMA guidelines"	Change agreed.

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271	3	Comment: The CAT should also be involved for an Advanced Therapy Medicinal Product. Proposed change (if any): and PRAC Rapporteurs as well as CAT rapporteur when the medicinal product is an Advanced Therapy Medicinal product.	Change agreed.
283-287	3	Comment: The CAT should also be involved for an Advanced Therapy Medicinal Product. Proposed change (if any): The CHMP Rapporteur, in co-ordination with the PRAC Rapporteur and the EMA procedure manager (PM) and if applicable the EMA product lead (EPL), taking account of CHMP comments, the PRAC outcome and the full scientific debate within the PRAC and the CHMP, for an Advanced Therapy Medicinal Product the CAT outcome and the full scientific debate within the CAT and the CHMP, and the conclusions reached, prepares the final renewal assessment report, which, once adopted by the CHMP, becomes the CHMP renewal assessment report and is appended to the CHMP opinion.	Change agreed.
308	1	**Comment:** Propose to keep in this guideline, the text mentioned in the previous version, which mentioned that a recommendation to renew the marketing authorisation under normal circumstances is possible in exceptional cases during the renewal.	

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		Proposal: To add "During the renewal, as for any other annual re-assessment, it will be evaluated if the grounds for the granting of a marketing authorisation under exceptional circumstances remain or not. In exceptional cases, if no such grounds remain, a recommendation will be made to renew the marketing authorisation under normal circumstances."	MA granted under exceptional circumstances are not expected to revert to a full MA, thus the Agency considers that it is not required mentioning such option in this guideline that provides the general principles for processing the renewal of centralised marketing authorisations.
313	3	Comment: The CAT should also be involved for an Advanced Therapy Medicinal Product. Proposed change (if any): submit the requested data to the CHMP and/or the PRAC and/or CAT Rapporteurs and Members as applicable	Change agreed.
322	1	*Editorial comment* **Comment**: As for previous paragraph, need to clarify that the reference to Annex II is to annex II of the Commission Decision. **Proposed change (if any):** They will be classified either as conditions imposed on the marketing authorisation in Annex II of the Commission Decision.	Change agreed.
367	1	*Editorial comment* **Comment:** Typo in sentence **Proposed change:**	Change agreed.

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		"….of its intention ~~of~~ to request a…."	
389	1	**Comment:** Propose to mention the review of the EPAR by the MAH before it is published (in accordance with the EMA policy EMEA/45422/2006 on deletion of commercially confidential information)	No review by the MAH is foreseen as the EPAR is updated with standard statements confirming the renewal of the marketing authorisation and the grounds for a potential additional renewal.
397	1	**Comment**: No details on validation phase are provided. In particular the timelines for validation of renewal submission would bring more clarity in procedural aspects and facilitate planning.	Change agreed. The following was included in section 3.2 Timetable "*Upon receipt of a technically valid application, the Procedure Manager responsible for the product will perform the validation of the content of the application. Supplementary information may be requested in order to finalise the validation.*"
398	1	**Comment**: As part of the update, the involvement of the Co-rapporteur in the joint AR is no longer listed. Please confirm that renewals do not need co-rapporteur involvement.	The co-rapporteur is involved at the commenting phase. The joint AR will be issued by the CHMP and the PRAC rapporteurs.
398, 399, 400, 401, 402, 407, 408, 409, 410, 411	3	**Comment:** The CAT should also be involved for an Advanced Therapy Medicinal Product. Proposed change (if any): to add the CAT in the renewal timetable.	Change agreed
398 and 411	1	**Comment:** As mentioned in EMA website (Questions and answers: renewals http://www.ema.europa.eu/ema/index.jsp?curl=pages/regu	A note * was included in the Annex 1 of the guideline to identify documents shared with the MAH. Furthermore, details of the process are included in the Questions and Answers related to

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		lation/q_and_a/q_and_a_detail_000038.jsp&mid=WC0b01ac0580023e7c), during the Day 60 and Day 96, the MAH will appreciate receiving the AR and revised AR. Receipt of mentioned ARs should remain in the guideline. As it will allow to start preparation of the answers to potential outstanding issues and to better understand the background of the remaining issues so that any oral hearing can be prepared and conducted more efficiently. **Proposed change:** "Day 60: Circulate to EMA, CHMP and PRAC members and MAH." "Day 96: Circulate to CHMP and PRAC members and MAH."	Renewals and published on the EMA website
405	1	**Comment:** Propose to mention the clock stop in the timetable. **Proposed change:** "- If outstanding issues*: adoption of List of Outstanding Issues with clock stop."	This is not in line with the standard timetable for the other procedures published on the EMA website. Please note that the detailed timetables with the dates for the renewal procedures published at the EMA website foresee two options 30-day assessment - after immediate submission of responses and 30-day assessment - after clock-stop for submission of responses.
412	1	**Comment:** Previously the guidance noted a possible oral explanation at Day 120: "Adoption of CHMP opinion. Possible oral explanation by MAH". Can it be clarified why the possibility for an oral explanation is removed in the draft guidance?	Details related to oral explanations fall under the general guidance to Applicants /MAH for oral explanations at EMA http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/200

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		Proposed change (if any): Please do not delete "Possible oral explanation by MAH".	9/10/WC500004673.pdf
412	1	**Comment**: The step for CHMP discussion seems to have been omitted. **Proposed change**: Day 120 **Discussion at CHMP** Adoption of CHMP opinion.	Change agreed. Step included
470	1	**Comment**: If no changes are being proposed the guidance should state that a clean word version of the SmPC, Annex II, outer and inner labelling and Package Leaflet in English should be provided.	Change agreed. The paragraph was amended as follows: "*A clean version of the SmPC, Annex II, outer and inner labelling and Package Leaflet in English has to be provided. In addition a word version highlighting potential changes proposed by the MAH should also be included in the application*"
482	3	Comment: EMEA has been replaced by EMA. To correct the abbreviation Proposed change (if any): "In case the MAH wishes to receive EMA feedback on their…"	Change agreed.
520	1	**Comment:** Additional text to reflect current practice **Proposed change (if any):** Alternatively, active hyperlinks to the current specifications	Change agreed

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		and formulation may be given.	
526 - 528	1	*Editorial comment* **Proposed change (if any):** product taking into account any new non-clinical data accumulated since the granting of the initial MA or the	Change agreed
533	3	Comment: to change MAA by MA Proposed change (if any): safety/efficacy data accumulated since the granting of the MA or the last renewal,	Change agreed
534-536	1	**Comment:** Revised text is proposed to align with the guidance on Addendum to clinical overview, lines 191-198: *This addendum should consist of a critical discussion addressing the current benefit/risk balance for the product on the basis of a consolidated version of safety/efficacy data accumulated since the initial MAA or the last renewal, 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 applicable. New signal assessment and new potential or identified risks raised during the renewal period that have not been subject to previous assessment (e.g. in PSURs) should be clearly highlighted in the data provided*. **Proposed change (if any)** It should address the current benefit-risk balance for the product ~~on the basis of~~ taking into account the PSUR data and safety/efficacy data accumulated since the granting of the MAA or the last renewal, making reference to relevant	Clarification on this statement was included in the guideline.

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		new information in the public domain. The discussion should clearly reflect the presented data ~~previously included in the PSURs and the new data that have~~ and highlight new signal assessment and new potential or identified risks raised during the renewal period that have emerged since the DLP of the last PSUR up to the DLP of the renewal.	
546	1	**Comment:** The Agency in this draft guidance has replaced the "90 days prior to renewal submission" wording with the "DLP of the renewal". However, this replacement has not been consistently implemented throughout the guidance (please refer also to line 595) **Proposed change (if any)** or since the last renewal until ~~90 days prior to renewal submission~~ DLP of the renewal	Change agreed. The wording has been aligned through the guideline.
550-551	1	**Comment:** Revised text is proposed to align with the guidance on Addendum to clinical overview, lines 196-198: *New signal assessment and new potential or identified risks raised during the renewal period that have not been subject to previous assessment (e.g. in PSURs) should be clearly highlighted in the data provided*. **Proposed change (if any)** ~~Actions taken from the DLP of the last PSUR up to the DLP of the renewal should be clearly identified and highlighted.~~	The changes made to the Reference Information should be differentiated from the Overview of signals.
553-554	1	**Comment:** It appears (from the proposed language) that only significant changes included in the PSURs should be mentioned instead of all relevant changes to the Reference Information had	Although all the changes should be included in the dossier, the MAH should specifically highlight the changes introduced after the PSUR assessment for

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		during the reporting period. **Proposed change (if any)** In this section, it should be clearly identified the changes ~~included in the PSURs~~ made during the reporting period of the renewal.	cases where this assessment is within the Renewal period.
554-555	1	**Comment:** Revised text is proposed to align with the guidance on Addendum to clinical overview, lines 196-198: *New signal assessment and new potential or identified risks raised during the renewal period that have not been subject to previous assessment (e.g. in PSURs) should be clearly highlighted in the data provided*. **Proposed change (if any)** ~~and the new changes made from the DLP of the last PSUR up to the DLP of the renewal.~~	The changes made to the Reference Information should be differentiated from the Overview of signals.
571-572	1	**Comment:** Revised text is proposed to align with the guidance on Addendum to clinical overview, lines 196-198: *New signal assessment and new potential or identified risks raised during the renewal period that have not been subject to previous assessment (e.g. in PSURs) should be clearly highlighted in the data provided*. **Proposed change (if any)** ~~New data since the DLP of the last PSUR up to the DLP of the renewal should be highlighted.~~	The changes made to the Reference Information should be differentiated from the Overview of signals.
580-581	1	**Comment:** Revised text is proposed to align with the guidance on Addendum to clinical overview, lines 196-198: *New signal assessment and new potential or identified risks raised during*	Initial wording maintained

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		the renewal period that have not been subject to previous assessment (e.g. in PSURs) should be clearly highlighted in the data provided. **Proposed change (if any)** Evaluation of new signals completed and new potential or identified risks raised during the period from the DLP of the last PSUR to the DLP of the renewal should be clearly highlighted.	
585-588	1	**Comment:** Include sentence used in prior paragraphs that instructs MAH to highlight new data since the last PSUR. Proposed change (if any): Add statement "New data since the DLP of the last PSUR up to the DLP of the renewal should be highlighted".	Addressed throughout the guideline
585-588	1	**Comment:** Clarify whether the patterns of medication errors and potential medications summary would be included under the section in the current guidance "Patterns of Use that are relevant to the Safety of Product"	This information could be integrated at the end of the section on findings or as separate section.
589-592	1	**Comment:** Proposed change (if any): Add statement "New data since the DLP of the last PSUR up to the DLP of the renewal should be highlighted".	Addressed throughout the guideline
595-596	1	**Comment:** The Agency in this draft guidance has replaced the "90 days prior to renewal submission" wording with the "DLP of the renewal". However, this replacement has not been consistently implemented throughout the guidance (for	Change agreed. The wording has been aligned throughout the guideline

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	Outcome ***(To be completed by the Agency)***
		instance, please refer also to line 546) **Proposed change (if any)** initial marketing authorisation or since the last renewal until ~~90 days prior to renewal submission~~ DLP of the renewal.	
600	1	Revised text is proposed for clarity. **Proposed change (if any)** safety, efficacy and effectiveness findings that arise after the DLP of the renewal but during the period	Agreed