30 September 2015

Submission of comments on 'Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the **conditional marketing authorisation** for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004’ (EMA/CHMP/509951/2006, Rev 1)

Comments from:

| Name of organisation or individual |
| --- |
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*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
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|  | EFPIA welcomes the revisions to the Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation (CMA) for medicinal products for human use falling within the scope of Regulation (EC) No 726/ 2004.The relatively small number of CMAs indicates a revision to the guidance is needed in particular to increase the applicability in the oncology field and beyond. While the system would benefit from changes of regulatory and scientific approaches, EFPIA is convinced that there is a need for a **renewed holistic perspective on CMA** in combination with and demarcation to other regulatory tools (full authorisation, PAES/PASS, etc.).In summary, EFPIA highlights the below key criteria for a successful guideline and additional more specific enablers, which will be followed by more detailed line-by-line comments:* A product which fulfils the **unmet medical need** criterion for an application for a conditional marketing authorisation could be viewed as automatically falling under the criterion of ‘**major interest from the point of view of public health and from the point of therapeutic innovation**’ allowing a request for an accelerated assessment procedure.
* EFPIA believes it is important that applications for a conditional marketing authorisation automatically qualify for an **accelerated assessment procedure upon request** from the applicant and proposes further amendments to Section 4.4 to support this.
* EFPIA welcomes the expansion of the definition of **‘seriously debilitating disease by** including ‘well-established major impact on patients’ day-to-day functioning either already early in the course of the disease, or in the later stages’ as described in lines 94-99.
* EFPIA calls for clarification and a more flexible interpretation on what should be understood as **“comprehensive data”** as well as **“(less) comprehensive data**” in relation to situations where a CMA can be applied as well as flexible processes allowing case-by-case justifications and assessment.
* EFPIA also believes that other changes would allow to incentives applicants to submit CMA instead of it being used as a rescue pathway and expects the recently **announced PRIME (Priority Medicines) scheme** to enable this (amongst others):
* a more flexible dialogue with the authorities
* flexibility in terms of the timing of submission of some pre-clinical and pharmaceutical data.
* EFPIA also welcomes the **renewed interpretation for evidence generation** in demonstrating benefit/risk in order to obtain CMA (lines 120-123) while strengthening the criteria for the MAH to fulfil the specific obligations (lines 339-342).
* A **review of and report on the experiences** with the revised system latest within 1-2 years after adoption of the guideline will be important to allow adjustments in scope with expectations.
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|  | The above key criteria need to be underpinned in particular through clarification of the following enablers:* Once unmet medical need has been confirmed for a product and CMA has been obtained for molecules of the same class and same indication, the **“unmet medical need”** should not be considered to have been met as long as the status of the first product is still conditional. Once a full license has been obtained for subsequent applications the unmet medical need should be justified on and individual basis. There should be an appropriate level playing field considering the need to address overall public health objectives.
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|  | * EFPIA welcomes the update of the list of general and administrative requirements for the **annual renewal** (section 5.1) in particular concerning the addendum to Clinical Overview (ACO) that is no longer required. EFPIA does not follow why the requirements for the annual renewal (Section 5.1) should remain high. The revision of the guideline provides an opportunity to reduce administrative burden which should not be missed: The value of most of the requirements can be questioned in particular since most of the items are included in previous eCTD submissions (including PSURs) which are accessible to EMA and all CHMP members. Therefore, EFPIA continues to request to reduce the requirements for an annual renewal and only include those items which have changed and are critical to assess that the MAH is fulfilling its commitments (see lines 339-342).
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|  | * EFPIA welcomes the possibility to proceed to a normal marketing authorisation not subject to **specific obligations** without the need to submit a separate ‘switch’ application as included in the previous guidance (section 6). However, in line with the comments related to the yearly renewal, EFPIA would welcome further simplification for obtaining a full approval based on the fulfilment of all specific obligations associated with the conditional approval. Such specific obligations are subject to separate assessments for which CHMP opinions are rendered hence it would be possible for the CHMP to render a normal MAA based on the completion of the last specific obligation and therefore no separate switch application is required.
* In addition, EFPIA would welcome the possibility for EMA to reconsider the validity of some specific obligations based on the existing scientific knowledge and regulatory environment at the time of the CMA. Certain obligations may no longer be relevant or outdated because either scientific or medical knowledge has evolved from another source since approval or the understanding of the benefit-risk of the drug in the approved indication has been further complemented from knowledge gathering or analyses.
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|  | * EFPIA would also welcome additional EMA guidance as to how the principle on conditional marketing authorisations can apply to **Type II variation** (e.g. for new indications) and extension applications. This is considered not to require a legal change and such guidance could further detail how specific obligations could support a conditional approval. Even with a variation or an extension application the unmet medical need can be justified and could relate to seriously debilitating or life-threatening diseases justifying an approval within the same principles as currently outlined in the draft guidance.
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|  | Finally, in commenting on the draft guideline EFPIA makes reference to its “ Proposal for Options to Improve the Application of the Conditional Marketing Authorisation System in the EU (not requiring legislative changes)”:[http://www.efpia.eu/uploads/Modules/Documents/2015\_07\_10\_efpia-cma-options-for-improvement-(1).pdf](http://www.efpia.eu/uploads/Modules/Documents/2015_07_10_efpia-cma-options-for-improvement-%281%29.pdf) |  |  |

1. 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)* |
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| 59-61  |  | Comment:The previous paragraph that stated that CMAs do not apply to new indications has been removed. We would welcome confirmation that this implies that CMAs can now be applied to new indications and line extensions. If this is the case, further clarity on practical aspects would be welcomed (e.g. will this be applied per indication or for all indications in the same MA?) |  |
| 68-71 |  | Comment:While applicants are invited to notify EMA of their intention to request a CMA in the letter of intent, it is EFPIA’s understanding that this can be discussed later in pre-submission meetings as in many cases the company may not be in a position to have decided on this at time of the letter of intent |  |
| 75-77 |  | Comment: a complete reference to the Regulation EC 507/2006 would clarify the text.Proposed change:(Article 2 of Commission Regulation (EC) No 507/2006)(Article 4 of Commission Regulation (EC) No 507/2006) |  |
| 100-105 |  | CommentDecision 1082/2013/EU has been recently adopted with the intention of combating serious cross-border threats to health and includes, within its scope, “health emergencies of international concern” and the relevant medicinal products. This should be referred to in this chapter.Proposed change:Add After lines 100-105“2. Medicinal products to be used in emergency situationsA justification should be provided that the medicinal product is intended for use in emergency situations, in response to public health threats duly recognised either by the WHO or by the Community (Decision No. 2119/98/EC). A reference to the relevant WHO Resolution or Decision, or to the measures adopted by the Commission in the framework of Council and Parliament Decision No. 2119/98/EC should be provided.Medicinal products falling within the scope of Decision 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health also qualify as “medicinal products to be used in emergency situations” within the meaning of Article 2 of Commission Regulation (EC) No 507/2006” (addition of last sentence) |  |
| 112 |  | Comment: Please remove ‘Regulation’ from line 112Proposed change: The requirements for a conditional marketing authorisation *~~Regulation~~* are described in Article 4 of Commission Regulation (EC) No. 507/2006. |  |
| 122171253 and 254 |  | Comment:In reference to recent discussion across stakeholders (STAMP meeting), it is important that the CMA procedure is seen in positive manner. In the proposed draft guideline, the absence of data is always referred as a risk. The previous version was referring to uncertainty related to the absence of some data. In the same logic as for the risk management plan, missing data are not to be seen as necessarily a risk but as missing information or undefined certainty that could be managed through the specific obligations or post-follow-up commitment. Proposed change:“Risk” to be replaced by “uncertainty” |  |
| 124-130 |  | Comment:For all products falling under the scope of Article 2, it may be appropriate to allow the applicant to submit less comprehensive **clinical data relating to the safety and efficacy (clinical parts)** of the application dossier, i.e. data that are “less complete than normal”, whilst not being “incomplete” (refer to Recital 4 and Article 4 of Commission Regulation (EC) No 507/2006).EFPIA acknowledges the clarification on elements of comprehensive clinical data which do not need to be available at the time of authorisation.In addition, consistent with Article 4(1) a conditional marketing authorisation may be granted with less comprehensive **pre-clinical or pharmaceutical (including quality/CMC) data** only in the particular case of emergency (Article 2(2)). Yet, on this point also drugs falling under the scope of Article 2(1) and (3), by nature, justify a degree of flexibility at submission in order to allow for more timely applications. For those cases, EFPIA proposes to specifically define, on a case-by-case basis, what “comprehensive data” in relation to pharmaceutical or pre-clinical data entails following prior agreement from the CHMP, (Co-) Rapporteur and the EMA. This would allow for a more timely submission and give an incentive to applicants to submit via the conditional marketing authorisation. This possibility is currently not fully reflected in the guidance. Alternatively, some pre-clinical or pharmaceutical data not essential to allow regulators to establish the benefit/risk balance of the product could be submitted as an additional specific obligation to the conditional marketing authorisation as appropriate.*Line 124-130 (replacement):*“Products to be used in an emergency situation, in response to recognised health threats, may provide particularly important benefits, therefore higher uncertainties related to the absence of some data may be acceptable**.** Art. 4(1) states that in such cases a conditional marketing authorisation can be granted also if preclinical or pharmaceutical data are not comprehensive.Specific consideration will also be given to and applications will be assessed for what constitutes “comprehensive preclinical or pharmaceutical data” at the time of submission for cases which are not classified as being used in emergency situations. Each of thoseapplications will be assessed on a case-by-case basis,taking into account the respective health threats and expected effects of the product. In addition, consistent with Article 4 (1) of Regulation (EC) 507/2006 for all products within the scope of Article 2 the clinical data referring to the safety and efficacy can be less comprehensive than normally the case.”  |  |
| 131-134 |  | Comment:Clarification to avoid misreading.Proposed change:“The elements of the comprehensive data that are not available at the time of authorisation should be discussed by the applicant and their acceptability justified based on the strength of available results and taking into account the requirement for a positive benefit-risk balance. If justified, such elements that may be waived at the point of time of authorisation could include:….” |  |
| 145-156 |  | Comment:EFPIA conducted a root cause analysis on problems with the use of the conditional marketing authorisation tool. Across the cases analysed in the oncology sector certain scientific elements, i.e. the use of “overall response rate” and the application of single arm studies lead to complex scientific discussions and a more stringent alignment on those will be key for future overall attractiveness of the tool.Proposed change:Considerations for the establishment of beneficial effects should explicitly name and acknowledge some of the surrogate markers, such as “overall response rate” as well as specific study designs, such as single arm studies, as applied in the oncology area. |  |
| 131- (134) - 165 |  | Comment:The process for accepting less comprehensive data, the justification thereof would benefit from further clarification. Proposed change:  “The elements of the comprehensive data that are not available at the time of authorisation should be justified on a case-by-case basis and discussed by the applicant and their acceptability justified based on the strength of available results and taking into account the requirement for a positive benefit-risk balance. If justified, such elements could include (….)*New addition after line 165:*“Prior to submission, a mutual understanding of the data package that is planned to be included in the application should be agreed between the applicant, the (Co)-Rapporteur and the EMA. In case the applicant might foresee that relevant supplemental data will become available during the evaluation, details should be provided about timelines and how these supplemental data are considered of relevance for their conditional marketing authorisation application.In addition some pre-clinical or pharmaceutical data not essential to the establishment of the benefit/risk balance of the product could be submitted as an additional commitment (specific obligation) to the conditional marketing authorisation as appropriate.”  |  |
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| 135-144 |  | Comment: Please add to the list an example that is applicable for vaccinesProposed change:* Vaccines effectiveness data (having used immunogenicity data and/or data from a human challenge study at the time of authorisation)
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| 137 |  | Comment:In reference to the Medicines Adaptive Pathway to Patients (MAPPS) concept and the possible use of real world data as well as registries (which are suggested to be added and listed here), reference to data set instead of database would clarify the possibilities. Proposed change:“database” to be replaced by “data set” |  |
| 137-138  |  | Comment:“with the same endpoint(s) and in same population” reads inflexible and may not always be possible.Proposed change:“Same” to be replaced by “similar” |  |
| 138 |  | Comment:EFPIA would welcome clarification of the definition of “same population” as it can read in different ways and results in different situations: 1. Same line of treatment or
2. Different treatment line in the same disease or
3. Across different disease with the same biological target receptor (mechanism of action).

What would be important is how data and scientific evidences are bridged to support a full product assessment; by having more flexibility in the next clinical step this will help the specific obligations fulfilment.  |  |
| 141-144 |  | Comment: EFPIA recommends limiting the list of possible elements with less than comprehensive data to the most important ones, by removing the reference on sub-populations and impact on other medication. If further data is important for sub-populations or on the impact of other medications, and if these are the only missing elements to a comprehensive data set, the approval should not be classified as “conditional”. Instead, it could be classified as “standard/ normal” with respective post-approval commitments.Proposed change: delete: ~~further data in important sub-populations, e.g. patients with resistance or a particular biomarker that may be important, further data on impact of other medication, e.g., efficacy data with other co-medication for combination therapies.~~ |  |
| 152 |  | Comment:The expectation on benefits outweighing “any” uncertainties in relation to a conditional marketing authorisation seems unrealistic and inconsistent with the concept of a CMA.Proposed change:“Conditional marketing authorisation could be appropriate when an intermediate endpoint shows benefits that outweigh ~~any~~ the uncertainties about the extent of the clinical benefit it translates to, and when confirmation on the clinical benefits is still required.” |  |
| 153-156 |  | Comment:In line with the general comment above that CMA should be seen in a “positive way”, the paragraph starting from line 153 “it has to be also ....” to 156 could be added to the paragraph 157 to 161 to give a perspective of potential case where the submitted data would not need specific obligations; i.e. full approval. |  |
| 157-161 |  | Comment: In line with the above comment, the examples mentioned in this sentence should reflect the most important elements.Proposed change: Scenarios of establishing a positive benefit-risk balance with less than comprehensive data include also situations when comprehensive data would require other additional data (e.g. with longer duration, larger database or additional endpoints ~~more data on particular subgroups~~), but the benefits demonstrated with the available data outweigh the risks and it would be disproportionate from the public health perspective to delay the approval of the product. Furthermore, it should be clarified that this paragraph does not signal an intent that such products would in the future be granted a CMA by default. |  |
| 172-174 |  | Comment:What is the definition of “… beneficial effects are particularly strong for the respective endpoint” in this context? A harmonized language as compared to other EMA guidelines (e.g. Reflection paper on methodological issues in confirmatory clinical trials planned with adaptive design) would be useful.Proposed change:“it is expected that beneficial effects observed are partic*ularly clinically meaningful”.*  |  |
| 184 |  | Development of quality documentation is usually not final at the time of a CMA. There will often be a need to include pharmaceutical data obligations.Proposed change:~~“In emergency situations~~ (delete), specific obligations to provide comprehensive non-clinical or pharmaceutical data may also be required.” |  |
| 191-195 |  | Comment: EFPIA would welcome if EMA could specify in which document (e.g. the risk management plan) the explanation and rationale on what are the remaining questions and how fulfilment of the obligation will result in a resolution of these questions.  |  |
| 218-221 |  | Comment:The section “it is likely that the applicant will be able to provide comprehensive data” now includes a reference to the orphan medicinal product and the obligation “to consider the suitability of the data to be generated for confirmation of the orphan designation at the time of the conditional marketing authorisation”. EFPIA understands that following Protocol Assistance to agree on the level of evidence required to confirm the orphan designation (i.e. significant benefit), the data submitted for the conditional marketing authorisation would be sufficient for the confirmation of the orphan status at that time. Proposed change:Line 221: at time of **conditional** marketing authorisation. |  |
| 230 |  | Comment: Please consider development of a vaccine which is administered to healthy subjects instead of patientsProposed change (if any): * ***Study ~~Patient~~*** population and the number of ***subjects/***patients to be included
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| 247 |  | Comment:For clarity of the referenceProposed change:Also Article 4 paragraph 2 of the Commission Regulation EC No 507/2006 specifies that.... |  |
| 262-272 |  | Comment: The revised draft guideline provides clarification on fulfilment of unmet medical needs, and provides an additional situation when medicines that provide major improvements in patient care over existing therapies can be eligible in certain cases. However the guideline states “In exceptional cases …” which, however, does not seem to be opening up the eligibility to fulfil unmet medical need and thereby facilitating future uptake for CMA. By making reference to “improvements to patient care”, this section primarily captures the caregiver’s perspective. It would also be relevant to consider fulfilment of an unmet need from the patient’s perspective, which would be achieved by assessing improvements in health-related Quality Of Life. This would also allow to further align with the description of unmet need provided in the guideline on accelerated assessment (lines 90-99)Proposed change: It is suggested that “major improvement” should also include an improved safety profile of the medicinal product concerned.‘In justified cases, also major improvements to patient care or health related quality of life could provide a major therapeutic advantage, e.g. if the new treatment is expected to address serious existing issues including major safety improvements with treatment compliance or if the treatment allows ambulatory treatment instead of treatment in hospital only.’  |  |
| 269-272  |  | Comment:We welcome the close collaboration between CHMP and COMP in such a situations. A more dynamic and synergic collaboration will help avoiding recent case of delay. Clarification on timelines and impact on the COMP procedure would be welcomed. In addition, it would be helpful if the guidance could clarify the process regarding the maintenance of orphan designation report that is submitted by the applicant at the same time as the MAA. |  |
| 304-305 |  | Comment: Clarification regarding the section numbering. Proposed change: “Please see also section 4.1.2.(b) above regarding the scientific advice on development programme for products intended for conditional marketing authorisation and the recommended approach of prospective scenario building”. |  |
| 304320395 |  | Comment:Section to be correctedProposed change:Please see also section 4.1.2 (b) |  |
| 319-320 |  | Comment: Clarification regarding the section numberingProposed change: “To ensure consistency of application the response should address the elements set out in section 4.1.2.” |  |
| Line 329-330  |  | Comment:It would be helpful for the applicant to specify when during scientific review the CHMP assessment/acceptability of a request for CMA will be available,Proposed change: “If a conditional marketing authorisation is requested at submission by the applicant, the acceptability will be part of the scientific review (Day 120 Assessment Report).” |  |
| Section 4.4 |  | Comment: EFPIA believes it is important that such applications for a conditional marketing authorisation automatically qualify for an accelerated assessment procedure upon request by the applicant and proposes further amendments to Section 4.4 to support this.Proposed change: Applications which are submitted for a conditional marketing authorisation should on request of the applicant be granted an accelerated assessment based on the overlapping criteria described in Article 14(9) of Regulation (EC) No 726/2004 and Articles 2 and 4 of Regulation (EC) 507/2006 on the conditional marketing authorisation. |  |
| Section 4.5  |  | Comment: To ensure product information is tailored to the users, feedback from physicians and patients on the usability of the information should be collected to prove the added value of the information versus the increased complexity of information. Usually, a statement in the SmPC or package leaflet is not sufficient to explain a regulatory concept to lay persons.In order to provide adequate context around this concept, EFPIA believes that the EPAR is the suitable document to explain the regulatory concept of conditional approval and the scientific rationale for its application. A reference in the product information to the EPAR can ensure that full transparency is provided to interested parties. |  |
| 355-359  |  | Comment:Since PSUR (now the PBRER) include an assessment of the benefit/risk of the product periodically, timelines of specific obligations should, where possible, follow the PSUR timelines to avoid a double assessment. |  |
| 360 |  | Comment: The details for the timetable for a renewal have been removed. EFPIA believes this information was of value for applicants and requests re-introducing the timetable details should be considered.  |  |
| 367 |  | Comment:It would be helpful to specify for in cases where the applicant assesses that the timeframes agreed for the specific obligation needs to be modified, when and how the request for modification can be made. |  |
| 374-377 |  | Comment: The intention of this paragraph could be made clearer. It is assumed that should (in probably rare cases) the renewal assessment procedure and/or the Commission decision steps take longer than expected; the conditional marketing authorisation will remain valid although it may have passed the deadline for its validity (for example; a conditional marketing authorisation is valid until 6 May 2015 and the renewal application was submitted on time i.e. 6 months prior to the expiry of the authorisation; if the Commission Decision is received on 10 May 2015 the marketing authorisation was still considered valid between the 6 and 10 May). In addition, the previous guidance mentioned that: “the renewal decision will refer to the expiry date of the preceding marketing authorisation so that the renewed authorisation will be valid for 1 year from the date of the previous expiry”. It is suggested to re-introduce this information which is valuable for applicants and helps clarify the intention of the above paragraph. Proposed change: “In order to ensure that medicinal products are not removed from the market except for reasons related to public health, based on Article 6 (4) of Regulation (EC) 507/2006 the conditional marketing authorisation will remain valid until the European Commission adopts a decision following the renewal assessment procedure, provided that the renewal application has been submitted on time. Following adoption of a positive opinion, the Commission decision on the renewal will refer to the expiry date of the preceding conditional marketing authorisation so that the renewed authorisation will be valid for 1 year from the date of the previous expiry.” |  |
| Section 5.1  |  | Comment: The requirements and administrative burden for the annual renewal (Section 5.1) remain high while the value of most of the requirements can be questioned in particular since most of the items are included in previous eCTD sequences/submissions, which are accessible to EMA and all CHMP members. Therefore EFPIA reiterates its request to reduce the requirements for an annual renewal and only include these items which have changed and are critical to assess that the MAH is fulfilling its commitments Proposed change:Section 5.1 on Renewal – proposal to reduce the list of requirements e.g. 5.1.1 Summary of product characteristics, Annex II, labelling and package leaflet if revised5.1.2 Specific obligations; one interim report per obligation with the required details in order to allow the CHMP an evaluation of its progress. 5.1.3 Inclusion of information related to the fulfilment of a specific obligation within the yearly CMA renewal applicationwhere the due date for submission coincides with the renewal application. |  |
| 395 |  | Comment: Please update referenceProposed change:“… (see also section ***5.1.2. ~~3.2~~***).” |  |
| 401-402 |  | Comment:EFPIA would like to better understand this bullet point. What is meant with “data related to specific obligations” and what would be the scope of submission of such data on top of the interim report.Also, in situations when specific obligations are linked to clinical studies and no protocol specified interim analysis has been performed within the reporting timeframe for the renewal, the timing of data cut to be used for the interim report should be indicated. |  |
| 405-406  |  | Comment: For clarity, we would recommend specifying that the other submissions should relate to the medicinal product in scope.Proposed change: “Data included in other submissions for the medicinal product, but relevant to the benefit-risk balance of the product should be taken into account in preparation of the renewal application.” |  |
| Section 5.1.2, line 446 |  | Comment:In line with our comments on EMA Policy 70, we requests that the results of interim clinical study analysis are exempted from publication until the study has been finalised. This is important to retain the scientific integrity of the study and avoid statistical bias. |  |
| 396 and 464  |  | Comment:“… clinical expert statement … “In line with the request for simplification of the requirements and administrative burden, EFPIA assumes that a revised Module 2.5 together with an updated signature of the clinical expert would be considered sufficient to fulfil this requirement. |  |
| 462-465 |  | Comment: The requirements and administrative burden for granting full approval (Section 6) remain high while the value of most of the requirements can be questioned in particular since most of the items are included in previous eCTD sequences/submissions which are accessible to EMA and all CHMP members. Therefore, EFPIA continues to request to reduce the requirements for an annual renewal and only include these items which have changed and are critical to assess that the MAH is fulfilling its commitments (see lines 339-342).Proposed change:EFPIA would welcome further simplification of this process since the completion of all specific obligations and the related assessments are available for the CHMP. |  |

Please add more rows if needed.