European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON "CRITERIA FOR REQUIRING ONE ADDITIONAL FIVE-YEAR RENEWAL FOR CENTRALLY AUTHORISED MEDICINAL PRODUCTS – EMEA/131973/2006 "

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	EFPIA – European Federation of Pharmaceutical Industries and Associations	Belgium
2	LFB-Biomedicaments	France
3	MSD - Merck Sharp & Dohme (Europe) Inc.	Belgium
4	Schering-Plough Europe	Belgium
5	F. Hoffmann-La Roche Ltd	Switzerland

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW	OUTCOME
EFPIA wished to reaffirm the principle that a second renewal should be an exception and not the norm.	Agreed in principle.
EFPIA also continues to believe that there should be an appropriate regulatory process involving discussion with the MAH prior to any decision being taken for a second renewal. When such a second renewal is justified, this should be accompanied by a clear and appropriate regulatory process and appeal rights. We are concerned that the EMEA draft paper does not include any reference to process.	The intention of this paper is to set-out the possible criteria for requiring one additional renewal. Procedural elements are outside the scope of this paper. EMEA recommends MAHs to always include their views on the appropriateness of granting an unlimited validity in the renewal application, and to discuss this issue during pre-renewal-submission contacts with EMEA. Any CHMP/Rap views to require an additional renewal will have to be justified in the Rap AR and CHMP AR. MAHs have the option to appeal the renewal opinion (as for any other opinion).
In many cases the criteria proposed for considering requiring one additional five-year renewal laid out in the reflection paper are addressed using existing regulatory tools and monitoring methods. Furthermore these criteria would mean that products that have been approved for longer than five years and the MA has already been granted unlimited validity could be forced back into another 5-year renewal cycle because it belongs to a class which is undergoing review of a serious safety issue (A good example of such a safety issue affecting a class of drugs that only took prominence many years after the products were on the market is the suicidality issue with SSRIs).	Not correct. The decision to require one further renewal or not, is to be made at the time of the first renewal. If a MA has been granted unlimited validity, it can not be “forced back” into another renewal cycle.
LFB: If the risk/benefit ratio could be put into question, based on pharmacovigilance data, why to ask specifically for an additional renewal after 5 more years rather than to follow the product until the situation is solved and at this point renew the marketing authorisation. We think that the time for reassessment should be determined in case by case depending of the situation.	Not possible. The requirement for a 5-year renewal after the granting of the MA, is laid down in the EU legislation.

MSD believes that the request for an additional five-yearly renewal should be reserved for truly exceptional cases, as called for by Regulation (EC) 726/2004. Whilst Article 14.3 of the aforementioned Regulation justifies such an additional renewal on the "grounds of pharmacovigilance", the true intent of the legislator and concern of the Agency lies not in the pharmacovigilance procedures themselves but rather the safety data derived therefrom. The revision to the Community medicines legislation introduced a strengthening of pharmacovigilance procedures and an increase in the frequency at which updated safety reports must be submitted. As a consequence, the strengthening of pharmacovigilance and market surveillance has brought with it greater efficiency and speeds up the administration's decision-making and sanction processes as compared to the past. In our view, Directive 2001/83/EC, as amended, and Regulation (EC) 726/2004 provide sufficient legal instruments for authorities to conduct immediate risk/benefit assessments for any marketed product for which a particular safety concern is suspected. Specifically, according to Regulation 726/2004 Article 41.4 the Agency may at any time ask the MAH to forward data justifying that the risk-benefit balance remains favourable. Therefore, a second five-yearly renewal is not needed to address such concern. Safety information is constantly monitored and discussed during PSUR assessments and results from post-marketing studies are timely submitted and assessed through variation procedures. As such, we do not see the additional benefit derived by imposing an additional five-year renewal on a renewed MA and having to wait until the next renewal procedure to re-assess the product's risk-benefit. This only adds to the administrative burden.	As above + The possibility for a second renewal is laid-down in the EU legislation and is therefore an instrument available to the CHMP to perform a further risk/benefit assessment of the product at a defined point in time. This reflection paper lays down criteria for implementation of this legal provision

SPECIFIC COMMENTS ON TEXT		
BACKROUND		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	EFPIA: The use of the word 'criteria' implies that a further product licence renewal will be an automatic requirement should one or more of the criteria' be met. It would be better if it was indicated that the situations below represented factors that should be taken into consideration by CHMP when deliberating on the need for a further PL renewal or otherwise, rather than criteria for a Yes/No decision by the CHMP. **Proposed change**: Amend to: "The purpose of this document is to set out factors that should be considered by the CHMP when determining the need for an additional five-year renewal of the product……" Proposed factors "…….The following factors should be taken into consideration:"	Any decision on the need for a further renewal will always be taken on a case-by-case basis, based on particular pharmacovigilance considerations for the product concerned. The wording of the introduction will be amended to reflect that these are criteria/ factors which will be considered, when deciding on the need for a further renewal or not of the product concerned.
PROPOSED CRITERIA		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
	EFPIA: The title of this section should be changed to 'Introduction', as it sets the context for the paper, rather than addressing the proposed criteria as the section title suggests. **Proposed change:** ~~Proposed criteria~~ **Introduction**	There are 2 main sections in the document: 'Background' and 'Criteria/factors'. This paragraph is only a short introduction within the section on 'criteria/factors'.

[1] Where applicable

	EFPIA: It is not entirely clear from the current wording that an additional five-year renewal is considered a tool for helping to monitor the safety profile of a product. In order to ensure clarity and understanding, the paragraph should be re-worded to explicitly state this. **Proposed change:** In general, if the safety profile of a product should be closely monitored this could be obtained by any (or a combination) of the following methods: - requiring an increased PSUR frequency reporting and/or - requiring specific post-marketing studies and/or - CHMP could consider requiring one additional five-year renewal to provide an additional benefit-risk assessment	The paragraph already acknowledges that this is "a further tool". This proposal would present the additional 5-year renewal as an alternative to increased PSURs and PM studies, whereas the intention was to use the possibility of another renewal as a <u>further</u> (additional) tool to those measures, providing for a direct assessment of benefit -risk when this is justified.

1. PHARMACOVIGILANCE COMPLIANCE CONCERNS

Line no. + paragraph no.	Comment and Rationale	Outcome
First bullet	**EFPIA:** The reflection paper seems to suggest that pharmacovigilance compliance concerns could lead to an additional five-year renewal. Considering that · the draft reflection paper rightly indicates that pharmacovigilance compliance concerns can be addressed through a pharmacovigilance inspection and a requirement to submit PSURs with increased frequency, · a further Renewal is not anticipated to provide additional benefit or additional protection of patients, the paragraph on pharmacovigilance compliance concerns should not be included in the list of proposed criteria/factors for requiring one additional five-year renewal. **Proposed change:** Delete this section	Agreed. This concern should primarily be addressed by considering a PhVig Inspection and/or increased frequency of PSURs.

First bullet	**MSD:** We agree that Community legislation provides sufficient powers to Agencies to regulate drug safety effectively. But we believe that the renewal procedure offers no additional benefit to address concerns related to companies' pharmacovigilance compliance which could be enforced through pharmacovigilance inspections or increased PSUR reporting requirements. Compliance concerns usually relate to a company's overall system and seldom are product specific. Therefore, we don't see a direct link justifying a request for an additional five-year renewal for a specific product. In addition, Commission Regulation 658/2007 provides for measures to be taken in case of pharmacovigilance compliance concerns. Adding another renewal additionally would be a double penalisation of MAHs. **Proposed change:** Delete this section	As above.
First bullet	**Schering-Plough:** This item should not be addressed in this reflection paper. This section states that in case of concerns regarding the MAH's PV system, a PV inspection could be requested and PSUR could be required to be submitted with increased frequency. However these kind of requests can be made independently from the submission of a five-yearly renewal. Thus submitting a full renewal application (including administrative and CMC information) would not help addressing the above mentioned concerns.	As above.
First bullet	**Roche:** **Comment**: it is not clear for the reader whether pharmacovigilance compliance concerns would lead to an additional five-year renewal. Considering that the guideline describe other measures to monitor these kind of concerns (i.e. pharmacovigilance inspection and an increased frequency of PSUR submission), it is suggested to not include the pharmacovigilance compliance concerns under the proposed criteria for requiring one additional five-year renewal. **Proposed change:** To delete the sentence or to move it out from the current section.	As above.

2. LIMITED EXPOSURE		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
First bullet	**EFPIA:** A definition of "limited exposure" would be helpful.	Difficult to pre-define this to suit all products. It should be considered by CHMP on a case-by-case basis.
First bullet	**LFB:** Maybe there is a need to define what limited exposure is. For example which ratio of the target patient population potential (50%, 30%) to not need additional 5 years renewal.	As above.
First bullet	**EFPIA:** Recent marketing of a medicinal product results in increased PSUR reporting frequency rather than being a criteria for requiring an additional renewal. **Proposed change:** Delete first sub-bullet~~– recent marketing of the medicinal product~~	Yes, this is also acknowledged in the text. However, the spirit behind requiring a 5-year renewal is indeed to do this after 5 years of marketing experience (i.e. wide exposure), before considering a product MA for unlimited validity.
First bullet	**MSD:** Pursuant to Reg. (EC) 726/2004 Article 14(4) medicinal products must be marketed within 3 years in the Community or their license will cease to be valid. This means that at the time of the first renewal, all products will have been marketed for at least 2 years. In addition, exposure data from marketing in countries outside the EU is usually available. Experience with new indications is collected through RMP monitoring and increased PSUR reporting frequency. PSURs are accompanied by a scientific evaluation, particularly of the risk-benefit balance of the medicinal product. According to Reg. 726/2004 Article 41(4), the Agency may at any time ask the MAH to forward data justifying that the risk-benefit balance remains favourable. A renewal procedure as a further mechanism to assess a product's benefit risk profile seems to be redundant. Generally, we believe that this criterion is not a valid reason to request an additional renewal in itself. An additional renewal request is justified only if safety issues with potential impact on public health have been identified.	As above.

	Proposed change: 2. Limited exposure - 1st bullet - Please delete first bullet point	
First bullet	**Schering-Plough :** -limited exposure: The submission of a PSUR is sufficient to assess the B/R of a product and thus the submission of a renewal application is not needed.	As above.
First bullet	**LFB:** -recent marketing of the medicinal product. **Comment:** The date of the renewal could be defined at five years after the first marketing.	Not possible. The 5-y validity period of an MA is set-out in the legislation.
First bullet	**Roche:** - recent marketing of the medicinal product. **Comment:** to clarify what is considered 'recent time', considering the sunset clause provision. To reword the sentence	As above – adequate exposure experience should be available before considering a product for unlimited validity.
First bullet	**Roche:** A definition of "limited exposure" would be helpful.	As above.
First bullet	**EFPIA:** - limited use in a recently approved new indication. Comment: to specify that this apply only to major new indication (i.e. new indication covering a new patient population). **Proposed change:** - *limited use in a recently approved new indication* **should this new indication carry with it a well identified clinically significant patient safety risk association with the new indication that was not previously recognized in association with the original marketing authorization.**	CHMP will decide on a case-by-case basis for the product concerned, taking into account any major changes which may have occurred to the use of the product, and possible linked pharmacovigilance concerns. Proposed revised wording not agreed.
First bullet	**Roche:** - limited use in a recently approved new indication. Comment: to specify that this apply only to major new indication (i.e. new indication covering a new patient population). **Proposed change:** To reword the sentence	As above.

First bullet	**Roche**: "limited use in a recently approved new indication" If the same formulation of a drug is used to treat different indications it is difficult to determine its use in a specific indication since exposure is usually calculated (e.g. for the PSUR) either from sales data / bulk sales data (tonnage). **Proposed change:** Delete.	As above.
First bullet	**LFB:** -limited use in a recently approved new indication. Based on the new PSUR requirements, a recently marketed product or a product with a recent new indication (proposal to add) would still fall within the 6 monthly or yearly reporting frequency at the time of renewal. **Comment:** Therefore would not need an additional 5 years renewal if no risk/benefit ratio issue.	As above.
Third bullet	**LFB**: Medicinal product currently not marketed as it is intended only to be used in emergency situations, in response to public health threats duly recognised either by the WHO or by the Community (Decision No. 2119/98/EC). **Comment:** Here again: need to define exposure level to be able to assess safety upon regular use.	As above.

3. SAFETY CONCERNS		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
	EFPIA: This section should be deleted or at the very least the 3rd bullet should be deleted (see above general comments) There is a danger that the current phrasing within this section would lead to an interpretation that all newly-approved products will be deemed to need an additional 5-year renewal:	See below.

	- Products approved with a RMP that contains risk minimisation measures should not automatically lead to the need for an additional 5-year renewal. - In addition, most newly-approved NCEs will have 'post-marketing studies ongoing and/or planned and which are expected to yield important new safety data which could impact on the benefit-risk balance'. The data generated from these studies and the interpretation of the risk/benefit balance can and should be assessed by other means without the need to resort to an additional 5-year renewal. Furthermore, the availability of any new information may not coincide with the timing of the renewal and would be evaluated as a separate activity. A further Renewal is not anticipated to provide additional benefit or additional protection of patients. **Proposed change:** Please delete section 3 or clarify	
	EFPIA: It is considered that the concerns listed under Section 3 do not lead to the need for a further Renewal. As indicated, safety concerns could be addressed through a requirement to submit PSURs with increased frequency. Additionally, such concerns could be addressed through Risk Management plans. **Proposed change:** Please delete section 3	Not agreed. CHMP confirmed the appropriateness of this criterion. In addition to PSURs and RMPs, the additional renewal would provide for a formal opportunity to review effectiveness of these measures and review the benefit-risk balance of the product.
First bullet	**MSD:** We agree that safety issues with a potential impact on public health are valid reasons for requesting an additional five-yearly renewal. However, the example given is misleading, because risk minimisation plans include both routine and additional risk minimisation activities. The effectiveness of these activities will be adequately and actively monitored through updates to the risk management plan. Routine risk minimisation activities usually include specific labeling statements in the product information to highlight safety measures to physicians and patients. This may be applicable for many products and we disagree that additional renewals should be routinely requested in such cases.	Text will be amended to refer to 'specific risk minimisation measures', to exclude those with only routine measures.

	Please change: "Medicinal products with a particular safety issue which could impact on the benefit risk balance of the product ~~e.g. those for which specific measures need to be taken and which need to be monitored in order to manage the risks (risk minimisation measures)~~."	
First bullet	**LFB:** A yearly reassessment until problem is solved could be more adapted.	Yearly reassessments are only foreseen for certain types of MA (MA under exceptional circumstances or conditional MA).
Second bullet	**MSD:** For most new medicinal products the conduct of post-marketing or specific outcomes studies are the rule. Results which yield important new safety or efficacy data which could impact the risk-benefit balance of a product are reported through PSURs and/or RMPs, plus (where applicable) through the Volume 9A requirement to promptly inform CAs. Usually these data are also submitted and evaluated through variation procedures in a timely fashion. There is no additional benefit to justify an additional renewal procedure. **Proposed change:** Please delete the second bullet	As above
Second bullet	**LFB:** Here again, why five years?	Unclear comment.
Third bullet	**MSD:** Class reviews of products are usually performed through Article 31 Referral procedures. A risk-benefit assessment is carried out as part of the procedure and specific measures may be taken as a consequence. This provides an adequate regulatory mechanism for monitoring the continued positive risk-benefit balance of a marketed product. Some products of a class may have already been renewed, some products may just be renewed and other products will only be renewed in the future. Depending on the life cycle phase of a specific product there may be unequal treatment of products in a class if such criteria are applied for requesting an additional five-yearly renewal. **Proposed change**: Please delete the third bullet	Not agreed. CHMP confirmed the appropriateness of this criterion.
Third bullet	**LFB:** Here again, why five years?	Unclear comment.

4. Other		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
	EFPIA: No comments on this section.	Noted.
First bullet	**MSD:** According to the CHMP GUIDELINE ON PROCEDURES FOR THE GRANTING OF A MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES, PURSUANT TO ARTICLE 14 (8) OF REGULATION (EC) NO 726/2004 a MA granted under exceptional circumstances will normally not lead to the completion of a full dossier and become a "normal" marketing authorization. This is not a valid reason for requesting an additional five-yearly renewal. **Proposed change:** Please delete the first bullet	Not agreed. CHMP confirmed the appropriateness of this criterion.
First bullet	**LFB:** Here again, would it not be better to adapt the time of reassessment and date of unlimited renewal in case by case?	As above – Review/ renewal timeframes are legally defined.
Second bullet	**LFB:** … could consider requiring one additional 5-year renewal taking into account the above-mentioned criteria… **Comment:** That would mean that the product is still not considered to have a "normal" MA. (contradictory)	Not agreed. Any other medicinal product with a full ("normal") MA is subject to the renewal provisions, incl. the possibility to require one additional 5-year renewal.
Second bullet	**LFB:** Proposes to add: Medicinal products for which clinical trials are planned / on going for other indication, other dosage, other route.	Not endorsed, as this is not a pharmacovigilance concern.