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

London, 23 February 2006
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# OVERVIEW OF COMMENTS RECEIVED ON QUESTIONS AND ANSWERS ON THE APPLICATION OF THE SO-CALLED "SUNSET CLAUSE" TO CENTRALLY AUTHORISED MEDICINAL PRODUCTS

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

| | Organisation |
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| 1 | Grand Public Association of the European Self-Medication Industry (AESGP) |
| 2 | European Generic Medicines Association (EGA) |
| 3 | European Federation of Pharmaceutical Industries and Associations (EFPIA) |
| 4 | IFAH-Europe (representing the European Animal Health Industry) |
| 5 | Merck Sharp & Dohme (Europe) Inc. |

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**Table 2: Discussion of comments**

| GENERAL COMMENTS - OVERVIEW | Outcome |
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| This draft guidance raises the same concerns as the draft guidance EMEA/180078/2005 (as a result of the definitions proposed in Section 4. of that draft guidance). We believe that the threshold for notification of a potential cessation of supply by the MAH has been set far too low.<br>The consequence of this will be that a huge number of unnecessary notifications to the competent authorities (consuming Agency and industry resources), while at the same time making it more difficult to identify occasions where there is a real potential for impact on the patient. Clearly the definitions for 'placing on the market' and 'cessation of placing on the market' must be the same for both guidance documents.<br>We believe that it would be helpful to include in the list of possible exemptions marketing authorisations granted prior to the introduction of the Article 58 procedure, which support marketing authorisations in markets outside the EU, and to provide further clarity on the procedure for obtaining exemptions for the Commission. | Please see outcome in the overview of comments on the Q&A "on notification to the EMEA of actual marketing and cessation of placing on the market for centrally authorised medicinal products" (EMEA/180078/2005), section 5.1 and the revised corresponding Q&A document.<br><br>The same definition applies for cessation of placing on the market for the purpose of both Articles 13(4) and 14(4-6) of the Regulation. The difference is in the threshold applied for both provision, one is at the level of the presentation, the other at the product level.<br><br>At this stage, no list of examples is intended to be published. It will be up to the MAH to justify why an exemption should apply (on public health grounds and in exceptional circumstances), and each justification will be considered on a case-by-case basis. As mentioned in the Q&A document, the request for an exemption is to be addressed to the Commission with a copy to the EMEA. |
| It is suggested that the two guidance documents (i.e. EMEA/180078/2005 and EMEA/180079/2005) are combined into one; this would be more user friendly and avoid duplication. | Two guidance documents have been set up separately as referring to the implementation of two separate provisions. Moreover, in the future, these two guidance documents will be integrated in the EMEA post-authorisation guidance. |

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| We appreciated the opportunity to comment to the draft post-authorisation guidance "Questions and answers on the application of the so-called 'sunset clause' to centrally authorised medicinal products" (EMEA/180079/2005).<br>We appreciate that this clause will only be applied prospectively. As the operation of the sunset clause has the potential to be an administrative burden for both the EMEA and the MAH, we would like to make some proposals to keep this burden to the minimum necessary. There are several aspects within the draft guidance that are unnecessary and simply create more work for everyone. | |
| • The presence of one presentation of one pharmaceutical form in one Member State is enough to 'fulfil' the sunset clause, i.e. that a product is on the market. Consequently it is overdone to report the actual marketing situation per presentation and per member state. | The requirements refer to two separate provisions of the legislation which have a different threshold of application. |
| • The reporting of <u>all</u> temporary cessation of being present on the market will lead to an unnecessary administrative burden: the wording should be such that unplanned and short temporary cessations are excluded (e.g. temporary out of stock situations). | See outcome in the overview of comments on the Q&A "on notification to the EMEA of actual marketing and cessation of placing on the market for centrally authorised medicinal products" (EMEA/180078/2005), section 5.1 and the revised corresponding Q&A document. |
| • Also the 2 months in advance notification will often be impracticable and impossible. Consequently, despite the fact that this deadline is mentioned in the legislation, it should be seen as a pivotal requirement necessary to fulfil the provisions of the sunset clause, unless there is a real risk to human or animal health from the absence of the product. | See outcome in the overview of comments on the Q&A "on notification to the EMEA of actual marketing and cessation of placing on the market for centrally authorised medicinal products" (EMEA/180078/2005), sections 5.2.2 and 5.3 and the revised corresponding Q&A document. |
| Please find below some specific comments to the mentioned guidance. | |

**SPECIFIC COMMENTS ON TEXT**

## 1. Introduction

| Section | Comment and Rationale | Outcome |
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| | We are far away from an established system were this way of reporting can be used. Thus, it should be clearly stated that hard copies and e-mails are acceptable. When electronic reporting via EVMPD will become feasible the Q&A documents can still be amended. | For the reporting until availability of the electronic system, a template will be provided by the EMEA and please see the revised Q&A document (EMEA/180078/2005) for the reporting modalities. |
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## 4. What are the Principles for the monitoring of the sunset clause provision?

| Section | Comment and Rationale | Outcome |
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| | We propose that the first sentence is re-worded as follows to provide additional clarity:<br>*"The marketing authorisation will remain valid if at least one presentation of the marketing authorisation is placed on the market* ***within*** *the Community* ***in one or more Member States,*** *including Iceland, Norway and Liechtenstein".* | Valid comment.<br><br>See amended wording in outcome below. |
| | We welcome the use of the Global Marketing Authorisation concept in the context of the sunset clause provision | Please note that the interpretation given for a marketing authorisation for centrally authorised products to remain valid in the context of the sunset clause provision has no relation with the notion of global marketing authorisation as referred to in Article 6(1) of Directive 2001/83/EC, as amended, and as defined in the revised Chapter 1 of the Notice to Applicants. |
| | For added clarity please amend the 1st sentence to read:<br>"The marketing authorisation will remain valid if at least one presentation of the marketing authorisation is placed on the market in the Community (in at least one member state) including Iceland, Norway and Liechtenstein." | Agreed |
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## 4.1 Marketing authorisation not followed by actual marketing

| Section | Comment and Rationale | Outcome |
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| | The proposed start date for the three year period for generic products is not consistent with the relevant text in Regulation 726/2004 (Art. 14.4), which states: "Any authorisation which is not followed by the actual placing of the medicinal product for human use on the Community market **within three years after authorisation** shall cease to be valid". | The principles on how to start counting after the granting of the marketing authorisation are based on clarifications given in the revised Chapter 1 of the NTA (section 2.4.2) and the "summary record of the 58th meeting of the Pharmaceutical Committee (1st June 2005)" - (section 6.) - published on the European Commission website on 10/10/2005. |
| | We suggest the sentence reads as follows: "However, for a generic medicinal product, the start of the three years period should be as of the end of the ten (or eleven) year period of market exclusivity **of the reference medicinal product** (I.e., the time when the generic fist can be placed lawfully on the market)." | Agreed |
| | We are pleased to receive clarification on the fact that, for a generic medicinal product, the start of the three-year period begins at the end of the ten (or eleven) years for data exclusivity, i.e. the date when the generic can be placed | In the text, the appropriate term "market exclusivity" is already used. |

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| | on the market. To be legally correct, the term "data exclusivity" should be replaced by "market exclusivity".<br><br>This interpretation, however, should be further extended to other circumstances when the generic medicinal products cannot be marketed, such as when a patent is still in force on when any other protection rules or other legal obligations such as litigation leading to injunctions are pending, as foreseen in point 6.1.1 of this guideline.<br>The second Paragraph should read as follows:<br>'For generic medicinal products, the start of the three-year period should begin from the end of the ten (or eleven) years of ~~data~~ **market** exclusivity, i.e. the date when the generic can be placed on the market **and at the end of other protection rules which must be respected**.' | Agreed as in line with the wording of the NTA, chapter 1, section 2.4.2 – see amended wording. |
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## 4.2 Medicinal product previously marketed no longer actually present on the market

| Section | Comment and Rationale | Outcome |
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| | If the sunset clause period is calculated only on the basis of the last date of release into a distribution channel, it will not take into consideration the specificity of products with large batch sizes and long shelf-lives (5-years). These products might well only be released into the supply chain once every five years. The EMEA must remember that multiple suppliers exist for generic products and that the volumes for each company are therefore much smaller. One batch may last for the entire shelf life. A similar problem can arise for so called niche products designed to treat limited patient populations but which have a relatively long shelf life.<br>The best date for calculating the sunset clause is, therefore, the date from which a product is no longer available for supply to wholesalers and hence to the patient.<br>In contrast to niche products, for frequently used products with numerous batches released to various markets, the MAH will be obliged to inform the EMEA about each and every batch release. A more reasonable and administratively less burdensome approach would be to inform the EMEA periodically that a given medicinal product has been placed on the market rather than immediately upon the release of every batch. This information will be available to the EMEA via PSUR anyway.*(Xref 6.1.2)* | The definition for the cessation has been discussed and agreed within the NTA group.<br><br>Moreover, there should be no confusion between the frequency of release into the distribution chain and the definition of cessation which is related to the last release into the distribution chain when the stock is going to be out to supply the patient. |
| | The definition of "cessation of placing on the market" must be consistent with that given in the guidance on notification to EMEA of actual marketing and | It is foreseen as mentioned in section 4.2, second paragraph, of the Q&A document that the definition of "cessation of placing on the market" and "no |

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| | cessation of placing on the market (EMEA/180078/2005).<br>As set out in our comments on the above draft guideline (i.e. EMEA/180078/2005), we believe that the currently proposed definition of "cessation of placing on the market", which triggers the start of the sunset clause period, is based on an overly simplistic approach to defining release into the distribution chain. | longer on the market" are the same.<br>The definition for the cessation has been discussed and agreed within the NTA group. |
| | The situation of IVMPs that could be subject to official batch release have to be taken into consideration, because official release could take considerable time. | See outcome in the overview of comments on the Q&A "on notification to the EMEA of actual marketing and cessation of placing on the market for centrally authorised medicinal products" (EMEA/180078/2005), in section 5.1. |
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## 5. What about Exemptions?

| Section | Comment and Rationale | Outcome |
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| | We believe it would be helpful to include in the list of possible exemptions marketing authorisations granted prior to the introduction of the Article 58 procedure, which support marketing authorisations in markets outside the EU. We therefore propose the addition of a third bullet, as follows:<br>• "*Medicinal products granted an EU Marketing Authorisation prior to November 20th 2005, where the EU authorisation is necessary to support authorisations in markets outside the EU*"<br>Another exemption should be possible for "regulatory" or "legal" reasons (even though these situations might be rare):<br>• "*Exemption may also apply when the MA holder or its representative can justify that it was not possible to place a product on the national market within 3 years due to the delays of national procedures such as reimbursement and pricing issues*."<br>It would be helpful to provide further information on the process for obtaining an exemption from the Commission (How is an application made? How long would determination of the application take? Would an exemption be valid indefinitely?). | At this stage, no list of examples is intended to be published. It will be up to the MAH to justify why an exemption should apply (on public health grounds and in exceptional circumstances), and each justification will be considered on a case-by-case basis. As mentioned in the Q&A document, the request for an exemption is to be addressed to the Commission with a copy to the EMEA.<br>These points have already been referred to the Commission. |
| | To avoid case-by-case discussions please include the necessity to provide EU documents for obtaining marketing authorisations in other countries, as an example for exemption of the sunset clause.<br>Again, in order to reduce the administrative burden: Products for which it is already known at time of registration that they will be/are only allowed to be | See outcome above.<br>It is acknowledged that in some cases, an exemption can apply from the granting of a marketing authorisation. Therefore, it is foreseen as stated in section 5 of the Sunset Clause Q&A, second paragraph, that MAH can request for an exemption at time of submission of the marketing application as appropriate which the |

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| | used in emergency situations should be excluded at time of registration from the requirement of reporting (could already be included in the Commission Decision); example: vaccine for classical swine fever | Commission will consider when issuing the Commission Decision. |
| | It would be helpful to provide further information on the process for obtaining an exemption from the Commission (how is an application made, how long would determination of the application take, would an exemption be valid indefinitely). | These points have already been referred to the Commission. |
| | At what point of time should a request for exemption be introduced to the Commission? (at any time, with the MA application?) | As mentioned in the section 5 of the Sunset Clause Q&A, it is acknowledged that depending on the type of medicinal product or the situation, an exemption might apply at any time of the life cycle of a product or even at time of submission of marketing authorisation application. Therefore, the MAH should address their request when appropriate. |
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## 6.1 When is the timer on?

| Section | Comment and Rationale | Outcome |
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| | During the interim period until the availability of the "sunset timer" in 2006, is an informal email for notification of the EMEA on the product level "marketed" or "not marketed" sufficient? | For the reporting until availability of the electronic system, a template will be provided by the EMEA and modalities of reporting are clarified in the revised Q&A document. |
| | As the information is public, there may be issues in the vet sector where the distribution chain is not as well standardized as in the human sector. The delay between the presence or the absence of the product in a country and the date of release or cessation of placing the product on the market may raise issues at the customer level. | This comment is rather related to the Q&A "on notification to the EMEA of actual marketing and cessation of placing on the market for centrally authorised medicinal products" (EMEA/180078/2005).<br>See outcome in section 6 of the overview of comments related to this Q&A. |
| 6.1.1 | The second part of the second sentence: *"... or when the MAH can legally place the medicinal product on the market considering the market exclusivity and other protection rules which have to be respected"* is not consistent with the relevant text in Regulation 726/2004 (Art. 14.4) which is unambiguous in defining the start date as the date of authorisation of the product. We believe that the draft guideline should be modified to reflect the relevant legal text. | The principles on how to start counting after the granting of the marketing authorisation are based on clarifications given in the Chapter 1 of the NTA (section 2.4.2) and the "summary record of the 58th meeting of the Pharmaceutical Committee (1st June 2005)" - (section 6.) - published on the European Commission website on 10/10/2005. |
| 6.1.1 | The last phrase of this section is troubling ("and other protection rules which have to be respected"). If this covers exclusivity granted to orphan drugs or paediatric PUMA's then this is fine (and should specify so). However, if this is intended to cover patent protection, then we oppose this last phrase (the 3 year clock should start from the moment the authorization validly allows the generic | See outcome above. |

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| | to be placed on the market, irrespective of the patent situation. If in this case the patent is to be taken into account, then why allow generics to apply for and obtain a marketing authorization after year 8 of the reference product's registration? | |
| 6.1.1 | For generic medicinal products the start of the three-year period should be calculated from the date when the generic can be placed on the market. Taking into consideration any period of market exclusivity or other protection rules which must be respected.<br><br>Although the information about market exclusivity is available to the EMEA, the information regarding other protection rules has to be provided by the MAH of the generic medicinal product. We suggest that the period for informing the EMEA of other protection rules not allowing the marketing of generic should be 60 days from the date of granting the MA. | Agreed as in line with the wording of the NTA, chapter 1, section 2.4.2.<br><br>Valid comment. This amendment is added in the revised Q&A document. |
| 6.1.2 | The definition of "cessation of placing on the market" must be consistent with that given in the guidance on notification to EMEA of actual marketing and cessation of placing on the market (EMEA/180078/2005).<br>As set out in our comments on the above draft guideline (i.e. EMEA/180078/2005), we believe that the currently proposed definition of "cessation of placing on the market", which triggers the start of the sunset clause period, is based on an overly simplistic approach to defining release into the distribution chain. | See outcome in the overview of comments on the Q&A "on notification to the EMEA of actual marketing and cessation of placing on the market for centrally authorised medicinal products" (EMEA/180078/2005), in sections 4.2 and 5.1. |
| 6.1.2 | *(Xref 4.2)* | See outcome in section 4.2. |
| 6.1.2 | We appreciate that a differentiation is made between intended and non-intended interruption of being on the market. If cessation is due to cases of 'force majeure', the MAH should not be the victim of this. The same applies for suspension of the licence until additional trials have been performed to comply with new legislation. | Acknowledged.<br><br>Unintended interruption like suspension is already listed as the case of "force majeure". |
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## 6.2 When is the timer off?

| Section | Comment and Rationale | Outcome |
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| 6.2.1 | Please add the word "any" so it reads "The sunset timer will stop running at the time of the first placing on the market of one presentation in **any** one Member State." | Not endorsed. |
| 6.2.3 | A ground for exemption from the sunset clause should be the requirement of | See outcome section 5. |

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| | third countries for the MAH to submit a FSC (free sales certificate). Without a licence in the country of origin (EU), a company is not able to market the product in some export countries, which will affect the health of the people in those countries. | |
| | ***Multiple marketing interruptions***<br>Please add a further paragraph to answer an additional question:<br>***Question:*** when the marketing of a product is interrupted or is stopped more than once, is the timer cumulative with the previous stops or not? Although the legislation clearly states "3-consecutive years", it would be useful to include this clarification as not all applicants read the legislation closely. | As it is clearly stated in the legislation, we do not see the need for further clarification to be provided in the Q&A. |
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## 7. What about the expiry of the sunset clause period?

| Section | Comment and Rationale | Outcome |
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| | ***Section 7***<br>We would suggest to add 'and the MAH' in the sentence below:<br>"*At the time of expiry of the sunset clause period, the EMEA will inform the European Commission* **and the MAH** *that the sunset clause provision applies…."* | Agreed<br>However, the MAH should be aware of the overall timing with regard to the sunset clause period for their product and for taking any appropriate actions, should they wish to retain the marketing authorisation. |