

21 December 2007

**APIC Comments on the Public Consultation Paper ‘Better Regulation of Pharmaceuticals: Towards a Simpler, Clearer and More Flexible Framework on Variations’ and the Draft Legal Proposal (Version: 24 October 2007)**

**GENERAL COMMENTS**

APIC fully supports the Commission’s initiative to modify the Variations Regulations and is very encouraged by the proposals put forward in this Paper. We acknowledge that they represent an important and positive step forward. However, we don’t believe that continuous improvement within the API industry will be achieved within this system; the proposals simply don’t go far enough. In order to stimulate change within the API industry, the responsibility for change implementation must be placed into the hands of industry through an assessment system based on performance (a “trust and verify” system). This system should allow companies to demonstrate their knowledge of the product and the manufacturing process, plus the good performance of their established cGMP systems, including change management, and in doing so, gain increased regulatory flexibility.

Having said that, we appreciate that experience in the implementation of the ICH Q8-Q9-Q10 principles needs to be gained before these can be fully embodied in the variations system. In light of this, when viewed as a short term solution, APIC welcomes and supports the Commission’s proposals, however, longer term, it is imperative that the ICH principles are fully embraced and that greater regulatory flexibility can truly be achieved by those companies who implement these principles.

With regard to the API industry, it’s not clear how much regulatory relief the proposals in this Paper will afford. In order for the Commission to achieve its objective of providing a simpler, more flexible framework for all stakeholders, the particular difficulties faced by the API industry must be addressed. For many API manufacturers, making a change under the current system is virtually impossible. If certain factors are not taken into consideration, the proposals will do little to alleviate this. In the following comments, an attempt is made under Key Item 3 to briefly explain how a change might be handled by an Active Substance Master File (ASMF) holder, including some of the hurdles that must be overcome. CEP holders can also face major problems when it comes to implementing changes, even though the change has already been approved by the EDQM. This is discussed under Key Item 4. APIC looks forward to meeting with the Commission in the new year to better explain these very important issues.

It should be noted that not all API manufacturers supplying the EU market are constrained by the current Regulations. Consider the very complex supply chains for APIs for a large section of the EU market for older, off-patent medicinal products – namely APIs entering the EU via chains of middlemen (traders/brokers). The implication is that the current Variations Regulations are completely unworkable for this sector, which in turn implies widespread non-compliance. The proposals currently on the table will certainly not solve this major problem.

Therefore we ask that the Commission pays serious attention to this issue. Resolving this matter will require a much more drastic reform of the Regulations.

In APIC's view, it is paramount that the Regulations are enforced through inspection. As long as no adequate API inspection system is in place to enforce compliance with the Regulations by all manufacturers supplying APIs to the EU market, the situation will continue to exist whereby companies who comply find themselves in a very unfavourable competitive position versus competitors who do not comply.

### **KEY ITEM 1: PURELY NATIONAL AUTHORISATIONS**

This item was covered by the previous "co-decision" Consultation Paper of 10 July 2007 on which APIC has submitted comments in September 2007.

### **KEY ITEM 2: ICH**

APIC fully supports the Commission's desire to support continuous improvement by providing greater flexibility to those manufacturers who implement the principles of ICH Q8-Q9-Q10. We appreciate that experience needs to be gained and so welcome the proposal to lay down the conditions for the classification of variations in a guideline rather than an annex to the Regulations to facilitate review.

It is understood that the Quality by Design approach will be extended to APIs, the basis of which will be the ICH Q8 guideline for APIs. Until this document is published, it is unclear how the notion of design space and other Quality by Design principles apply to APIs. Therefore, we are unable to comment further on this topic at this time.

### **KEY ITEM 3: "DO AND TELL" PROCEDURE**

APIC strongly supports the introduction of an annual reporting system for Type IA variations. However, the proposed procedure does not describe the option of submission of annual reports by ASMF holders. It is of utmost importance to the API industry that ASMF holders also benefit from this system. To this end, APIC would like acknowledgement of the need for direct contact between the competent authorities and the ASMF holder in order to keep the ASMF up-to-date and current. Already, since the adoption of the ASMF (previously EDMF) system, such direct contacts have always been a pre-condition to ensure the confidentiality of the AIM-Restricted Part of an ASMF. Not mentioning this aspect in relation to the new annual reporting procedure may lead to misunderstandings between stakeholders. We envisage that the ASMF holder would inform both the MA holder and the authorities of a Type IA variation at the time of implementation. The MA holder would subsequently include the change in his annual report at his discretion.

Currently, it is extremely difficult for an API manufacturer using an ASMF to make even a very minor change to a manufacturing process. Often, the ASMF is lodged with multiple authorities, supporting multiple MAs, held by multiple MA holders. When an ASMF holder wants to make a change, he must first obtain the support of all MA holders as they are the ones who must submit the variation applications. Often the change is blocked at this stage because not all MA holders will agree to it. The flow diagram in Appendix I shows the steps the ASMF holder must go through before he can implement a change. Remarkably, even a Type IA variation can take up to 2 years to complete because of the number of MA holders / authorities involved. This situation is made far worse by the fact that some authorities insist on a Type II variation for all changes impacting the AIM-Restricted Part of a ASMF, even for a very minor change, because the MA holder is not in possession of all the information (due to confidentiality issues) and therefore cannot declare that all the conditions are met. The MA holder could, however, obtain this declaration from the ASMF holder if the Regulations would clarify that this is permitted. As a result, API manufacturers who use ASMFs to protect their confidential know-how are penalised and are prevented from making even the smallest changes despite the fact that they are fully GMP compliant and have excellent quality systems. It would be unacceptable if, under the new system, a change could be classified as annual reportable for a company who does not use an ASMF but a Type II variation for one who does, despite the fact that the two companies may have comparable quality systems.

If it will be clarified that ASMF holders are allowed to utilise the annual reporting system as APIC envisages, some of the difficulties described will be alleviated. The direct contact between the ASMF holder and the authorities is crucial in order for the ASMF holder to fulfil his responsibilities in accordance with the commitment made in the Letter of Access (see CPMP/QWP/227/02 Rev 1 Annex 2). In addition, in a multi-customer / multi-authority environment, a new or existing customer may submit a new MAA at any time so it is essential that the ASMF is up-to-date and current. Also, a customer may initiate a Mutual Recognition Procedure at any time so it is essential that all authorities have the same current version of the ASMF.

#### **KEY ITEM 4: WORKSHARING**

APIC strongly supports the concept of worksharing.

Regarding timelines, the review periods should correspond to those proposed for that particular variation type, e.g. the review period for Type IB variations should not be extended to 60 days. Also, there should be a timeline for issuing the acknowledgement of receipt of a valid application. This is currently missing from the draft proposal.

APIC would also like clarification on how the worksharing will work in practice, e.g. what information will EMEA require to assess the change if they are not in possession of the original submission? Regarding changes to ASMFs, will the EMEA require the whole ASMF or just the relevant sections?

Regarding the avoidance of duplication of work, there are at least two situations faced by many ASMF holders that have not been addressed in the draft proposal:

1. A change to one ASMF may be submitted by multiple MA holders, each with multiple products, and therefore may be assessed multiple times (see Figure 1 in Appendix II).
2. One change can affect multiple ASMFs (see Figure 2 in Appendix II).

Another example of duplication of work that could be avoided is the re-assessment by the competent authorities of changes to CEPs which have already been approved by the EDQM. It is proposed in the Consultation Paper that a line extension that involves the introduction of a new API (Annex I paragraph 1 (a) of the draft legal proposal) should be downgraded to a Type IB variation if a positive opinion is received from the EMEA through the worksharing procedure. It follows then that the submission of a new or revised CEP that has already been through the EDQM's rigorous assessment procedure should never be more than a Type IB variation. However, currently, there is a major flaw in Variation 15 Condition 2 that means that situations can arise where the submission of a new or revised CEP results in a Type II variation. If uncorrected, this will continue to obstruct many changes in API manufacture that are aimed at improving quality, improving safety, lowering costs and protecting the environment. We are aware that a full revision of the detailed guideline will take place at a later stage in 2008 but yet – though maybe a bit premature – we would like to anticipate that by highlighting this important, specific problem through a detailed explanation in Appendix III. We look forward to discussing this matter further during the coming year.

Furthermore, APIC strongly believes that if a change to a CEP dossier has been assessed by the EDQM and does not result in a change to the CEP itself, a revision of the CEP should not be issued. Currently, this practice is causing vast numbers of pointless variations. Please note that APIC is not suggesting that the MA holder is not informed that a change is being made. On the contrary, APIC realises that this is vital; however, it is inappropriate to use the variation system as a means of doing this.

#### **KEY ITEM 5: TYPE IB BY DEFAULT**

APIC strongly supports the proposal that variations which are not explicitly recognised as Type IA, Type II or line extensions are handled by default as Type IB variations. However, the statement in the introduction to the detailed guideline (page 27 of the draft proposal) that “a variation which is classified in this guideline but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of Type II” seems to be at odds with this. The same default principles should apply.

Also of concern is the safeguard clause whereby a competent authority can evaluate a variation according to the Type II procedure if they consider that it has a “substantial potential to have a negative impact on the quality, safety or efficacy of the medicinal product”. While APIC understands the need for a safeguard clause in case of a serious risk to patient health, the wording must ensure that this clause is not misused. Type IB variations should only be reclassified as Type II in exceptional circumstances and the grounds for this must be justified. An appeal system should also be introduced.

In addition, the timeline proposed for obtaining a scientific recommendation from the EMEA for an unclassified variation (60 days) is too long. Currently a recommendation can be obtained in 1-2 weeks. This timeline should be maintained.

## **OTHER PROPOSALS**

### **Classification of Variations**

As stated under Key Item 2, APIC fully supports the replacement of the current annexes by detailed guidelines on the conditions for classification of variations. We look forward to participating in the development of these guidelines in the next round of consultation.

### **Grouping Variations**

APIC strongly supports the introduction of grouped variations.

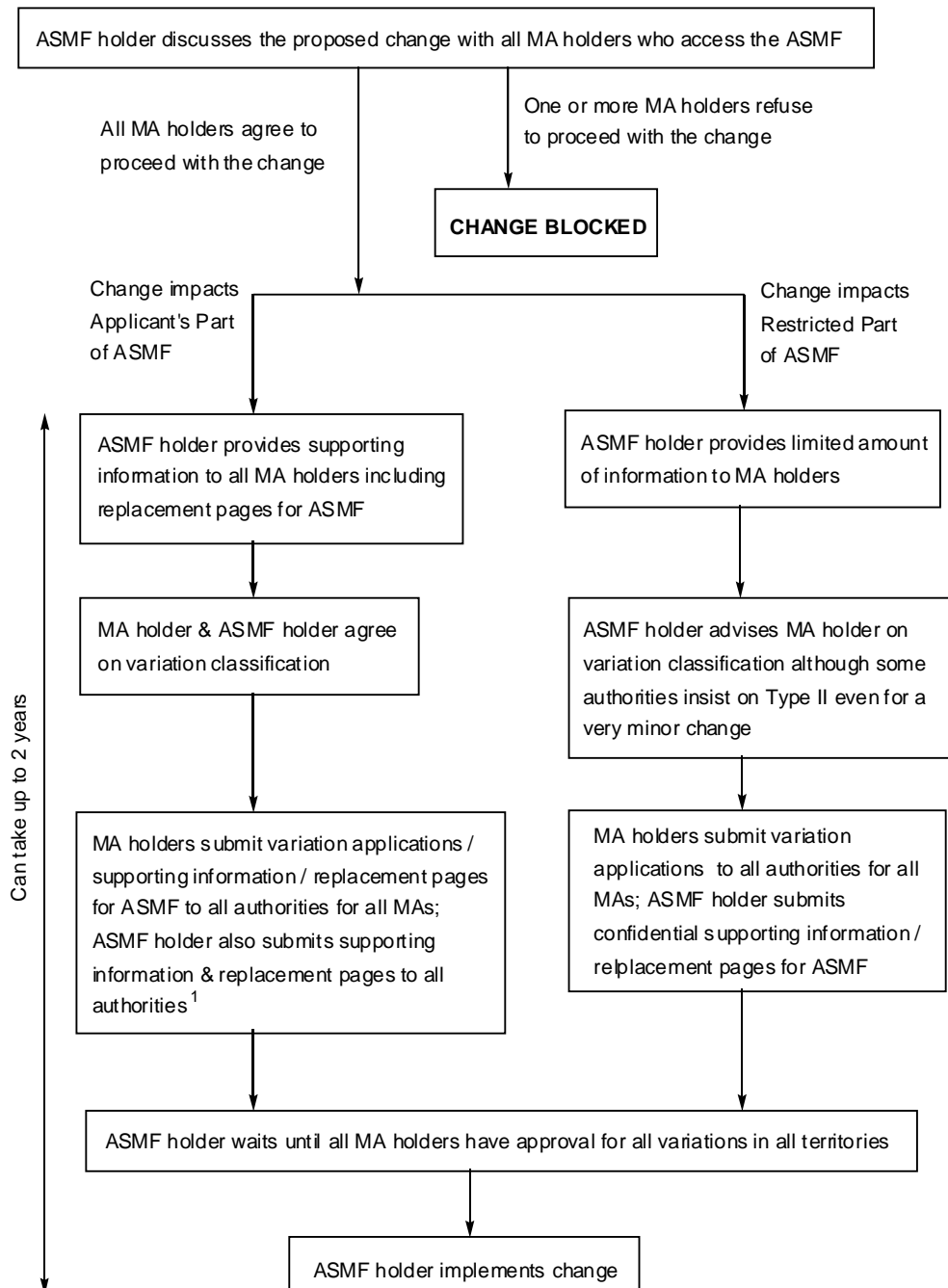
Regarding point 6 in Annex II, this should include the active substance, i.e. the option to group variations should also apply to changes which relate to a project intended to improve the manufacturing process and the quality of the active substance.

## **POINTS NOT ADDRESSED IN THE CONSULTATION PAPER**

A glossary should be included in both the Regulation and the guideline as not all terms are clear.

### APPENDIX I

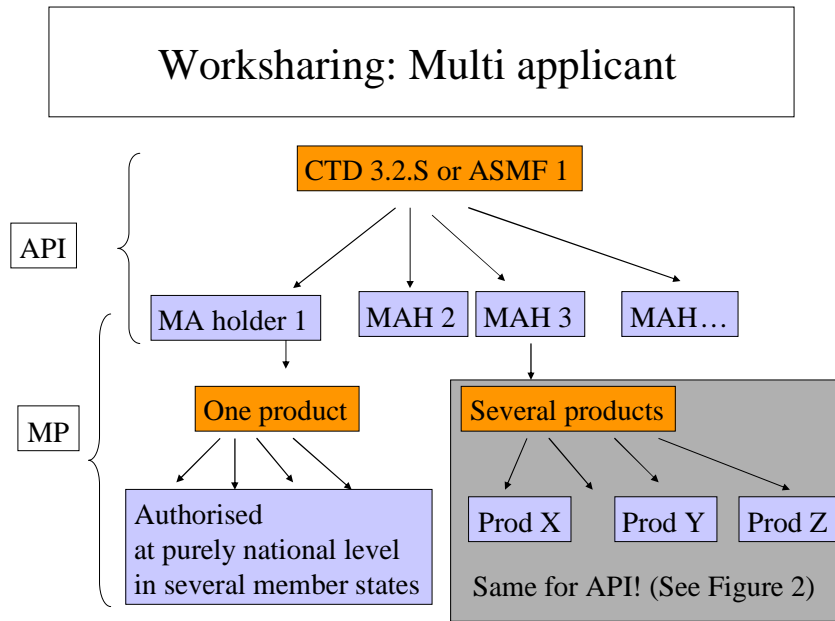
#### Example of how an API manufacturer handles a change to an ASMF



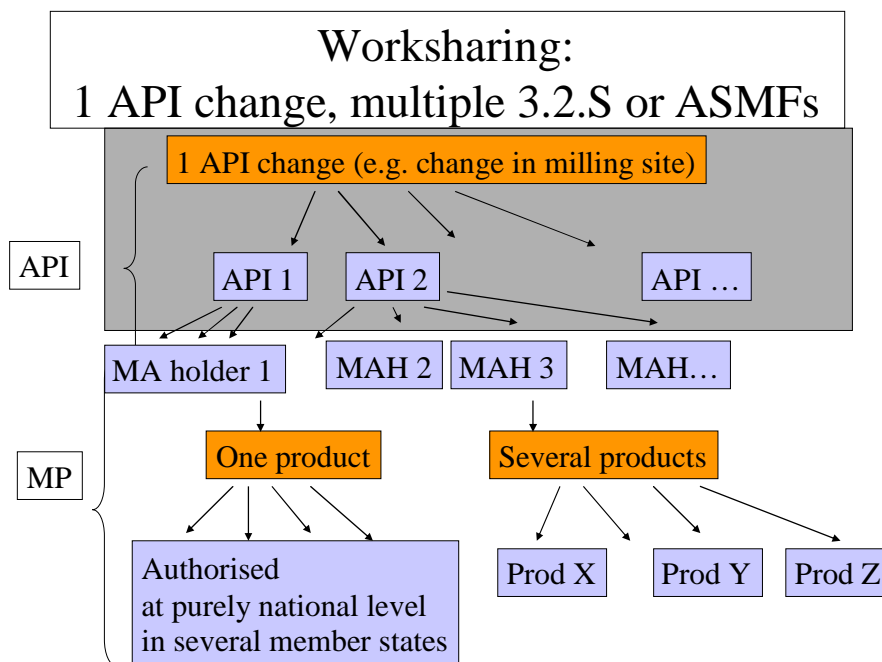
<sup>1</sup> in accordance with the commitment made in the Letter of Access (see CPMP/QWP/227/02 Rev 1 Annex 2)

**APPENDIX II**

**Figure 1**



**Figure 2**



MP Medicinal Product

### APPENDIX III

#### **Variation 15 Condition 2: An important issue that should be resolved within coming discussions on the detailed guideline**

According to Condition 2 regarding Variation 15, as included in the current Regulations, a Variation will be classified as Type II if the submission consists of a new or a revised CEP that includes changes in the specifications for impurities.

Further clarification on how this Condition 2 should be interpreted was published subsequently by the Commission and by the, what was then called, Mutual Recognition Facilitation Group (now CMD). As can be seen hereunder, these documents make clear respectively that the Type II option only applies to additions of specifications for new impurities and that the Type II option does not apply when the (new) impurity is a residual solvent within the ICH Q3C's Option 1 limits:

#### **Notice to Applicants: Guideline on dossier requirements for Type IA and Type IB notifications (European Commission, July 2003):**

##### **Added Note to Variation 15:**

The reference to unchanged specifications for impurities, if applicable, in condition no. 2 should refer to new additional impurities. In notification no. 10 on minor change in the manufacturing process of the active substance, condition no. 1 stipulates that there is no change in the qualitative and quantitative impurity profile or in the physicochemical properties. In notification no. 12 on change in specification of active substance tightening of specification limits or addition of new test parameters are allowed. One of the conditions for these changes to qualify as a type I notification is that the change should not be the result of unexpected events during manufacture. The conditions of these notifications should be borne in mind in the fulfilment of the conditions of notification no. 15.

#### **Q/A-list for the submission of variations according to Commission Regulation (EC) 1084/2003 (MRFG, March 2005):**

**Question 20.** *If a new or updated CEP is submitted or a DMF is replaced by a CEP (variation #15) what should be done if conditions #1 and/or #2 (specifications are unchanged and product specific impurities are unchanged) are not met?*

**Answer:** A Type II variation has to be submitted because condition number 1 and/or number 2 are not met. In the event that the only change regarding the specification for impurities is a change in the residual solvents that is in compliance with the ICH-limits (Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95)) and where the relevant Option 1 limit is applied to Class 2 solvents, no Type II variation is necessary and the change may be submitted according to Annex I.

However, though these exemptions improved the situation to a certain extent, the remaining situations that are yet being classified as requiring Type II Variations continue to obstruct many important and beneficial improvements in API manufacture.

In addition, we find this requirement a highly disproportional one because all safety issues regarding the change in impurity specifications have already been thoroughly assessed within the CEP dossier assessment process at EDQM making yet another duplicate assessment through the by far most burdensome type of Variation procedure unnecessary, unjustified and unrealistic.

***Detailed explanation and an example:***

Procedures and time frames

Submission to EDQM of a new or amended CEP dossier on a process change that results in a change in impurity specifications on the CEP (while “non-exempted” by above referred documents) triggers an assessment process at EDQM that on average will be at least as thorough and lengthy as a Type II Variation assessment procedure.

A regulatory requirement to have this followed by Type II Variations by all users of the CEP (MA holders using the API for their dosage forms) implies that the lengthy EDQM procedure is followed by numerous major Variation assessment procedures per customer / MA combination.

It is very important to stress that MA holders will normally be very reluctant to enter into Variation Type II procedures at all in situations such as these.

In conclusion, such regulatory barriers will in most cases cause possible process improvements to be aborted already in an early evaluation stage. Therefore these unnecessary barriers to progress and improvement should be avoided.

Assessment

All safety aspects of the change in impurity specifications are thoroughly evaluated within the CEP dossier assessment at EDQM. This includes e.g. assessment of extensive safety study reports on the impurity, when relevant.

After such thorough and comprehensive assessment a Variation submission of at most Type IB would be justified and duplication of extensive assessment work should be avoided.

An Example to illustrate the problem

This example is based on a real life situation and is in many ways representative for frequently occurring situations:

An API manufacturer has developed green, environmentally friendly technologies for the manufacture of a number of its APIs. The change over to the new technologies will be very beneficial to society in general, to patients and also to the manufacturer itself for a number of reasons:

- Enormous decrease of the use of environmentally unfriendly and hazardous chemicals
- Very large decrease in energy use
- Spectacular improvement of the quality of the APIs because most impurities, including all or most residual solvents, will not be present anymore in the API since they are not used anymore in the new manufacturing processes
- Improved stability of the APIs
- Decrease in production costs

The resulting purity is of an unprecedented high level for the involved APIs: All impurities that are present in the API produced in the classical manner are either completely absent or their levels have decreased drastically. However, there is one exception: Because of the use of enzyme technology a new specification is added:

*“Residual protein: less than 50 ppm”*

Because of the significantly changed technology new CEPs must be obtained via the submission of new CEP Dossiers. The total assessment period at EDQM until issuance of new CEPs for each of these Dossiers is around 18 months. The submissions include extensive study reports proving that the included limit for residual protein is safe and justified and e.g. cannot lead to any allergenicity issues.

However, when contacting its numerous customers (MA holders) on switching from the classically produced APIs to the ones produced via green technologies the customers point out to the API producer that the appearance of the new impurity specification implies that Type II Variations will have to be submitted for all their involved MAs, even though the Type II procedure for this situation is obviously fully out of proportion from a scientific perspective. Many of these customers conclude that the efforts and costs required for this make the proposed switch very unattractive to them. Therefore, the APIs manufactured through an environmentally friendly process have great difficulty in gaining a market share in the EU.

***Proposal for resolving the issue:***

In order to come to a reasonable and workable solution for this issue it will be necessary to make some adjustments to the text for Variation 15 and its Conditions.

We propose the following revised text (see next page):

**15. Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance**

<b>a. From a manufacturer currently approved</b>	Conditions: 1, 2a, 2b, 4 (see below)	<b>IA</b>
	Conditions: 1, 2a, 4	<b>IB</b>
<b>b. From a new manufacturer (replacement or addition)</b>		
<b>1. Sterile substance</b>	Conditions: 1, 2a, 2b, 3, 4	<b>IA</b>
	Conditions: 1, 2a, 3, 4	<b>IB</b>
<b>2. Other substances</b>	Conditions: 1, 2a, 2b, 3, 4	<b>IA</b>
	Conditions: 1, 2a, 3, 4	<b>IB</b>
<b>c. Substance in veterinary medicinal product for use in animal species susceptible to TSE</b>		
	Conditions: 1, 2a, 2b, 3, 4	<b>IA</b>
	Conditions: 1, 2a, 3, 4	<b>IB</b>

Conditions:

1. The finished product release and end of shelf life specifications remain the same.
- 2a. Unchanged additional (to Ph.Eur.) product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
- 2b. Unchanged additional (to Ph.Eur.) specifications for impurities, if applicable (Taking into account the exemptions as defined in “NOTICE TO APPLICANTS, GUIDELINE ON DOSSIER REQUIREMENTS FOR TYPE IA AND TYPE IB NOTIFICATIONS” (July 2003): Note to Variation 15 and the Answer to Question 20 in “Q/A-LIST FOR THE SUBMISSION OF VARIATIONS ACCORDING TO COMMISSION REGULATION (EC) 1084/2003”, Mutual Recognition Facilitation Group, March 2005).
3. The active substance will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability, or if data to support a retest period is not provided.
4. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

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