

<p align="center"><b>MEMBER STATE AGREEMENT UPON CONDITIONS UNDER WHICH THE RMS CAN START THE MRP/DCP</b></p>
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## **LEGAL BACKGROUND**

The provisions in the legislation are silent regarding the period after receipt of an application and start of the procedure as Article 28(2)(3) and (4) of Directive 2001/83/EC as amended only lay down:

### **28(2)-Concerns MRP**

*...The reference Member State shall prepare or update the assessment report within 90 days of receipt of a valid application...*

### **28(3)-Concerns DCP**

*...The reference Member State shall prepare these draft documents within 120 days after receipt of a valid application...*

### **(28(4)-Concerns finalisation of MRP and DCP**

*... Within 90 days of receipt of the documents referred to in paragraphs 2 and 3, the Member States concerned shall approve...*

## **BACKGROUND/ HISTORY**

MS have since the possibility of MRP (and later DCP) agreed upon a so-called *validation period* in which the practical aspects are taken care of before assessment takes place e.g. receipt of dossier, unpacking of the same, recording of the application in NCA systems and databases and identifying whether or not the application should be accepted for assessment etc.

The *validation period* is described both in the Notice to Applicants, Volume 2A (current version February 2007), Chapter 2, Section 3.3.2 and in several of the CMDh agreed papers.

The CMDh paper *Procedural Advice: Automatic Validation of MR/Repeat-Use/DC Procedures* (current version March 2009) highlights that the validation period is a 14 days period which is starting when all CMS have received the application (for DCP) or both application and RMS assessment report (for MRP and Repeat-use procedures).

In several places it is also mentioned that the 14 Days are considered as calendar days.

However, practice through the years, has shown that the RMS has not been able to start a procedure after 14 calendar days due to numerous invalidation issues raised by the CMS involved in the procedure.

It would be in the interest of all the NCA's involved to improve cooperation during validation, as this uncertainty on procedure start has an impact on the resource allocation in the RMS. It has also been remarked by the European pharmaceutical industry associations that the numerous validation issues raised often makes the procedure start for MRP and DCP very unpredictable and has an impact on their resource allocation.

Several initiatives to improve the common understanding of validation issues and to reach an agreement on how to tackle validation issues have been promoted by the CMDh. One of the initiatives was to create a CMDh ad Hoc Group on Validation Issues/National Requirements. As one of its tasks, this group developed a paper on *Regulatory and Administrative Dossier Check-in during the Validation Phase for New Applications/ Extension (December 2008. The introductory note of this paper clearly defines what should be done during the validation:*

*“The validation check is a verification that the application meets the administrative and legal dossier requirements in accordance with the current legislation. This is a check on the documentation in Module 1 and confirmation that Modules 2 to 5, as appropriate are present. All necessary documentation will be checked to ensure it is physically present in the dossier and that the information is complete and correct. No scientific evaluation of the documentation/dossier can take place as part of the dossier check-in procedure”.*

This paper was adopted by the CMDh at the December 2008 meeting.

Other initiatives of the ad Hoc Group included publishing papers with the primary goal to emphasise the importance of taking care in the compilation of the dossier and highlight the Applicant's responsibility to ensure that the application is fully valid on submission to each Member State in order to minimise (or better avoid) procedure start delays.

Validation and improvements in the validation process has also been a theme at Industry-CMDh meetings.

Although many efforts have been made to improve the validation to ensure start of procedures to comply with the agreement that the Validation period is a 14 calendar days period, Member States still struggle to meet the deadlines for Validations.

## **THE SITUATION TODAY**

We are still faced with issues which would be post procedure and/or scientific issues being raised by MS during validation. Examples are Braille declaration, discussions on naming of the product, how to state the strength of the product, labelling of the device being part of the product, questioning the justification for a biowaiver, the justification for absence of readability test, request for signed national translations of SmPC, PL and labelling, signed declaration of intended pack sizes and pack types to be marketed, requests for commitments concerning details on the national phase (post approval).

Also, the discussion on the legal basis is subject to repeated discussions in the CMDh as a validation issue in connection with submitted applications although we should all respect the ECJ ruling in Case C-452/06 (Synthon BV case).

It should beyond this be noted that according to the European Pharmaceutical Industry Associations, Additional National Requirements remain an important issue to be solved as it seems that many of them are not listed in the published table "*Data requested for New Application in the MRP/DCP which are not stated in the current EU legislation and/or in Volume 2B, Presentation and format of the dossier Common Technical Document(CTD) and/or in the EEA approved guidelines/Recommendation papers*"(current version April 2010).

## **RESOURCES IN NCAs**

Although the NCAs are organized in different ways it is worth noting that objection(s) raised from a Member State inevitably result in resources spent from all other involved Member States (archiving of e-mails, archiving of supplementary information, verification of additional applicant submissions, update of the documentation package, repeated RMS validation status check-up etc.).

Resources in some NCAs may today also be scarce.

For this reason a proposal for a new concept should be introduced.

## **HMA/CMDh TASK FORCE**

As many of the common validation issues mentioned above are minor and not critical for starting a procedure and in order to streamline the validation of new applications the *HMA/CMDh Task Force on Availability of Resources at NCAs for MRP and DCPs* decided to propose giving the RMS more power to start a procedure even if one or more MS involved have raised minor issues, which could be solved during the procedure (agreed at WP meeting in Bled, Slovenia, in January 2010). Agreement on this principle and the conditions to be set out should also be sought in HMA.

Following the Bled meeting in January 2010 the CMDh has expressed willingness to work for implementation of the above principle and furthermore, validation will also be part of the discussion in the CMDh sub-group on the Future of the CMDh.

The Chair of the TF presented the principle at the HMA Joint meeting held in Seville, Spain on 12-13 April 2010 and the HMA endorsed the development of further operational improvements of the MRP/DCP such as the proposal to establish those conditions under which the Reference Member State can start the procedure after Validation.

## **STREAMLINING THE VALIDATION PERIOD**

The proposal is to streamline the 14 day validation period, by dividing the raised issues into validation issues and non-validation issues. The validation issues have to be solved in validation

and the non-validation issues, which should not hold up start of a procedure, will be handled in a structured manner during the procedure.

An important note is that **no** change is proposed with respect to the timelines for validation. The validation period is 14 calendar days and starts when all CMSs has received the application (for DCP) or both the application and the RMS assessment (for MRP and Repeat-Use procedures). The RMS also still, at Day 7, notifies the CMSs who have not completed the CTS record stating that the application is valid.

It is though the duty of all MS that they follow the timelines given in the CMDh “*Procedural Advice Automatic Validation of MR/Repeat-use/DC procedures (current version March 2009)*” and not prolong the Validation period by not being prepared to validate or by not confirming when previously raised issues have been resolved.

Member States also have to state the reason for their Invalidation and not just state in the CTS e.g. *Validation is pending*.

The RMS is also not allowed to backdate the start of the procedure.

#### **The principle as stated in the agreed paper**

***Regulatory and Administrative Dossier Check-in during the Validation Phase for New Applications / Extensions (December 2008) still also apply.***

#### **Validation issues – No procedure start**

*A MS/CMS can only invalidate and prevent start of the procedure if one of the following conditions is not met:*

- If parts of or the complete dossier according to the legislations requirements are missing e.g. Annexes to the Application Form , ASMF/incorrect version of the ASMF, Letter of Access, no Manufacturing Authorization provided
- If parts of or the complete dossier are not in English, or translations e.g. M2 documents or GMP Certificates
- Dossier not in the national language and/or insufficient number of copies submitted according to the NCAs published requirements
- If the format, media or number of copies are not acceptable/missing, cf. the requirements for electronic submission published by the NCA
- If fee is missing or incorrect fee paid according to the NCAs regulation
- If the data exclusivity period for the reference medicinal product has not expired
- If the chosen reference medicinal product has not been approved according to the Community acquis

- The chosen legal basis does not fulfill the criteria according to the current legislation and/or the reference medicinal product is stated incorrect<sup>1,2</sup>
- Non-compliance with the requirements of the Paediatric Regulation (where applicable)
- If the product used as reference product in the bioequivalence/therapeutic equivalence study(ies) with the notion of global marketing authorization differs from the chosen reference medicinal product
- The RMS is awaiting the necessary minimum information on the European Reference Medicinal Product and/or the full composition of the used Reference Medicinal for the demonstration of bioequivalence (Where applicable)
- If not all Additional data requested, cf. **published** Table “Data requested for New Application in the MRP/DCP which are not stated in the current EU legislation and/or in Volume 2B, Presentation and format of the dossier Common Technical Document(CTD) and/or in the EEA approved guidelines/Recommendation papers”(current version)” have been met by the applicant

#### **Non-validation issues– RMS empowerment to start the procedure**

*The RMS can start the procedure although the following issues still haven't been solved on Day 0 (the applicant still has the duty to rectify the missing/incorrect documents):*

- If **Non published** Additional national data is requested. Beyond **published** Table “Data requested for New Application in the MRP/DCP which are not stated in the current EU legislation and/or in Volume 2B, Presentation and format of the dossier Common Technical Document(CTD) and/or in the EEA approved guidelines/Recommendation papers”(current version)”
- A MS states in the CTS Validation pending without given any reason
- If the CMS start the evaluation and raise scientific evaluation issues such as labelling of the medicinal product, questioning the applicants submitted justification for a biowaiver, the submitted justification for absence of readability test, requests for updated manufacturers authorization/GMP Certificate as the submitted is expired/close to expire
- Mock-ups(may be fulfilled during the assessment period)
- Specimen( samples of API and/or medicinal product) or a declaration that they will be sent are missing (may be fulfilled during the assessment period)

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<sup>1</sup> MS should respect the ECJ ruling C-452/06 and it is strongly recommended to bring different views between MS to the attention of the CMDh for discussion, to ensure a consistent approach from all Member States.

<sup>2</sup> It should be noted that successful passage through the initial validation phase does not preclude subsequent refusal, on grounds of non-compliance with the legislation or absence of satisfactory supporting data, at any other stage of the procedure, which become apparent on further consideration of the dossier cf. Article 26.2 of the Directive 2001/83/EC as amended.

- The name of product stated in the Application Form and the Cover Letter should be the same (strongly recommended cf. CMDh Cover Letter Template but not a validation issue)
- Statement that the applicant/MAH will submit printed documents within X days upon request of the MS
- Module 1.3.5 Product Information already approved in the Member States (as only in national language)
- Original signature of Experts in Module 1.4 (may be fulfilled during the assessment period)
- Table of Content in Module 2.1 is missing
- The Introduction in Module 2.2 is missing
- The DDPS Declaration Form is missing
- Environmental risk assessment for a generic or a justification for a waiver is missing
- Declaration(s) from the Qualified Person's concerning GMP compliance has been enclosed in annex 5.22 but the applicant has not used the new "Template for the Qualified Person's declaration concerning GMP compliance of the active substance used as starting material and verification of its supply chain "The QP declaration template""
- If the CMS raise **post procedure issues/commitments concerning the details in the national phase** (e.g. discussion of naming of the product<sup>2</sup>, Braille declaration, legal status of the product, request for signed national translations of SmPC, PL and labelling, signed declaration of intended pack sizes and pack types to be marketed,.

*It should be noted that these are only examples of non-validation issues. The list is not exhaustive and may be extended on an on-going basis.*

The RMS/CMS should clearly state during the validation phase if a raised issue is considered a 'validation issue' or a 'non-validation issue'. Should the RMS be in doubt whether an item is raised as validation issue or non-validation issue it is strongly recommended that the RMS liaise with the MS concerned before starting the procedure.

In exceptional cases, if an agreement between the RMS and the CMS cannot be reached both parties are encouraged to bring the issue to discussion at the CMDh meeting.

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<sup>2</sup> The Name of a generic product referring to a Centralised approved product has to be agreed at finalisation of the procedure.

### **Submission of responses to non-validation issues during the procedure**

#### *MRP/Repeat-use:*

For MRP/Repeat-use: The applicant has to have solved/fulfilled all pending non-validation issues by Day 30 at the latest.

#### *DCP:*

For DCP: The applicant has to have solved/fulfilled all pending non-validation issues by Day 50 at the latest.

*Responses to pending non-validation issues should be sent according to the NCAs practice.*

In both cases, if the applicant fails to submit in due time the CMS will bring the matter forward to the RMS/MS concerned and to the applicant in their Day 50 respectively Day 70PrAR/100 Comments.

**The applicant is asked to confirm in their day 60 response (MRP) or day 106 response (DCP) that all non-validation issues have been solved/fulfilled.**

*The CMDh will also monitor that applicants take their responsibility serious to submit fully valid applications.*