Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

CMD(h) BEST PRACTICE GUIDE ON THE COMPILATION OF THE DOSSIER FOR NEW APPLICATIONS SUBMITTED IN MUTUAL RECOGNITION & DECENTRALISED PROCEDURES

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1. INTRODUCTION

The objective of this Best Practice Guide (BPG) is to emphasise the importance of taking care in the compilation of the dossier for a Marketing Authorisation Application (MAA), to minimise delays in validation, to avoid invalidation of submissions, to forestall questions from Member States (both RMS and CMS), and to enhance the efficiency of the regulatory process.

This BPG provides a summary overview of points to consider at validation, together with a list of references as to where to find the advice. It does not replace any legislative requirements for validation or the recommendation to seek specific advice from Member States (MSs) prior to the submission, as necessary.

A validation step is required to identify MAAs that should not be accepted for assessment due to non-compliance with regulatory requirements. This is a complex step for National Competent Authorities (NCAs) and requires the applicant to consider and address potential validation issues before submission and to take account of national requirements in different Member States.

The applicant has an obligation to ensure that the application is fully valid on submission, in particular that the data are sufficient to fully support dossier requirements, the legal basis of the submission and the proposed product information. The submission of premature or incomplete dossiers, in an attempt to minimise regulatory timelines, is not acceptable and can cause procedural delays. 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.

2. SUITABILITY OF THE DOSSIER

The format and content of the dossier should comply with current regulatory and national requirements.[1, 2, 3, 4, 5]

The applicant should ensure that in-house quality assurance steps are in place to ensure that the submitted dossiers are the authentic, current editions and that they are consistent across modules.

Where, for good reasons, data are absent in some sections of the dossier, the applicant should ensure that a satisfactory justification is provided.

This should include, where appropriate, reference to Scientific Advice or other regulatory advice meetings with MSs (concerning the extent of the data provided in the dossier and/or other regulatory issues), and the completion of Module 1.2 Application Form, Section 3.2. For reasons of transparency, it is recommended to include copies of MSs Scientific Advice in Annex 6.14 of the Application Form. The applicant should discuss if the dossier is in compliance with the advice provided or highlight justified differences in Module 1.5 and elsewhere in the dossier, as appropriate.

A "*Notes to Reviewers*" document could be provided as an Appendix to the Cover Letter, providing further information in order to facilitate navigation through the dossier.

As required by Article 28 of the Medicines Directive[1] only identical dossiers should be submitted to each MS involved in MR/DC procedures. However, any additional data, which is specific to and is requested by a MS[4, 5] should be provided to that concerned MS in Module 1 "*Additional Data*".

3. LEGAL BASIS

The legal basis of the application has a profound impact on the extent and nature of the data provided in the dossier and it is therefore of critical regulatory importance. The same legal basis should be used in all MSs. It is recommended that the legal basis should be thoroughly discussed and justified in Module 1.5 and Module 2.

3.1 Article 10.1 and 10.3 Applications

The Reference Medicinal Product (RMP)
Applications made under Article 10 of Directive 2001/83/EC should include a discussion of the choice of reference medicinal product (RMP), including as necessary:

- its authorisation on the basis of a complete dossier in accordance with Articles 8.3, 10a, 10b, or 10c of Directive 2001/83/EC
- consideration of the relevant global marketing authorisation according to Article 6 of the Directive
- data exclusivity
- consideration where the reference product is no longer authorised.

If considered necessary, for example, if the date of first authorisation was before EU accession, the applicant should confirm with the relevant NCA from which date that authorisation was in compliance with the *Community aquis* (see also the CMD(h) website *FAQ on the Community aquis and data exclusivity for the reference product*[6]*).*

With reference to sections 1.4.2 and 1.4.3 of the Application Form, the RMP which is or has been authorised for not less than 6/10 years in the EEA, and the RMP authorised in MSs should form the same global marketing authorisation.

Non-Harmonisation Issues
In the case where the RMP is authorised in the RMS and CMSs, but the Summary of Product Characteristics (SmPC has not been harmonised across MSs, the CMD(h) advice "*Legal basis for generic applications when the indication(s) of the reference medicinal product differ between RMS/CMS(s)*" [7] should be followed.

In the case where the RMP (as the global marketing authorisation) is authorised in the RMS and CMSs, but without harmonisation of the marketed product strengths or pharmaceutical forms, then

the CMD(h) advice "*Interpretation and Member States recommendation for applications submitted according to article 10 when the strength and/or the pharmaceutical form of the reference medicinal product differs between RMS/CMS(s)*"[8] should be followed.

Article 10 allows the use of a European Reference Product (ERP), when the RMP is not authorised in one or more MS included in the procedure. In this case, the CMD(h) advice in "CMD(h) Working Document "*Information to be submitted by the Member State of the European reference medicinal product*"[9] should be followed.

Medicinal Products used in Bioequivalence or Therapeutic Equivalence Studies
The applicant should discuss and justify the study reference medicinal product used in bioequivalence or therapeutic equivalence studies in Module 1.5 and Module 2.

For Article 10(1) and 10(3) applications supported by a bioequivalence study, the study medicinal product should be included in the same global marketing authorisation of the RMP and be authorised in the EEA, in line with the Notes for Guidance CPMP/EWP/QWP/1401/98 "*The Investigation of Bioavailability and Bioequivalence*"[10].

For applications submitted under Article 10(3) and supported by a therapeutic equivalence study, the study reference medicinal product used in the therapeutic equivalence study should be authorised in the EEA.

If results from comparative bioequivalence/therapeutic equivalence studies are not included in the dossier, then their absence should be justified in Module 1.5.

3.2 Article 10a Applications

For applications made under Article 10a, the applicant should justify the eligibility of the drug substance to be of well-established use. In particular, the applicant should clearly show that the specific rules in Annex 1 of Directive 2001/83/EC[2] have been applied and met, and that the criteria in Chapter 1 of NTA Volume 2A are satisfactorily addressed[11].

If the dossier includes both published and own data, the submission would be considered a mixed marketing authorisation application and should be made under Article 8.3 of Directive 2001/83/EC.

3.3 Article 10b Applications

For applications made under Article 10b, the individual substances must have been authorised in the EEA, see NtA Volume 2A Chapter 1 Section 5.5[11].

3.4 Article 10c Applications

Article 10c applications are only possible if the reference product has been authorised under Article 8.3, 10a 10b or 10c for which there is a full dossier, according to the requirements of the NtA Volume 2A Chapter 1 Section 5.3[11], and authorised in the Member States concerned in the procedure. Further CMD(h) advice is provided in "*Informed Consent Applications in Mutual Recognition and Decentralised Procedures Recommendations*"[12].

4. OTHER ISSUES

To aid validation of the submission, the applicant should highlight in the Cover Letter any registration issues to MSs, in line with CMD(h) "*Member States recommendations on the cover letter for new applications submitted through the MRP/DCP*"[13]. A template for the cover letter is available on the CMD(h) website[14]. The information in the cover letter will be dependant on the type of application, but should include the following, as necessary:

4.1 Multiple/Duplicate Applications

The applicant should indicate in the Cover Letter if they are submitting simultaneously or subsequent duplicate applications. In the case of subsequent duplicate applications, the applicant should provide a reference to the initial application and confirm that the application referred to is updated according to the current legislation. Appropriate details should be given in Module 1.2 Application Form, Section 5.3. For further published advice, see "*Recommendations on Multiple/Duplicate applications in Mutual Recognition and Decentralised Procedures*"[15].

4.2 Responsibility for the application

The responsible person for the submission in each MS should be the proposed MAH in the RMS, or an alternative authorised by the same MAH, supported by appropriate documentation provided in Annex 6.4 of the Application Form.

4.3 Transfer of Ownership

If a transfer of ownership for the product is to take place in the national step after finalisation of the procedure, this should be supported by appropriate information in the Application Form and any additional documents required by individual MSs provided. For some MSs, once the procedure has started, transfer of ownership will not be possible until the procedure is closed and the licence granted to the originally proposed MAH. It is recommended to seek advice from the MSs concerned.

4.4 Manufacturing Authorisations for DC Procedures

Satisfactory manufacturing authorisations are required on initial submission.

In the case of EU sites, if absent, then it is the responsibility of the applicant to apply for an inspection to the relevant NCA in which the site is located. Without exception, the application for inspection should be sufficiently in advance to ensure that the inspection is complete and a manufacturing authorisation available on initial submission

In the case of non-EU sites, if absent, it is the responsibility of the applicant to apply for an inspection to the relevant NCA , which is the authority in whose territory the importing site is located. In case the NCA, for any reason is not able to carry out the inspection, this can be delegated to another EEA NCA.[16] The application for inspection should be sufficiently in advance of the MA application to ensure that the inspection is complete and a manufacturing authorisation available on initial submission. However, with a view to avoiding delays in the start of a decentralised procedure, the CMD(h) has agreed that in exceptional cases it should be possible to validate an application, where an inspection of sites outside the EU has not yet been carried out. The manufacturing authorisation has to be available for the restart of the procedure on Day 106[17].

If there is a Mutual Recognition Agreement (MRA) in place between the countries where the site is located and the European Community, the results of GMP inspections carried out by the MRA partner authority are normally recognised by the EU authorities[18].

4.5 Fee

Member States fees are subject to national rules, and fees errors are a common ground for invalidation. It is recommended that the applicant clarifies MSs fee requirements before submission, with reference to NtA Volume 2 Chapter 7[4]and relevant MSs websites.

4.6 Drug Substance Data

Active Substance Master Files (ASMF)
The applicant should confirm that the ASMF holder has submitted the full ASMF (Restricted Part, Applicant's Part and Expert Report/QoS) to each MS involved in the procedure. The applicant should also confirm with the ASMF holder that the Applicant's Part submitted in the application dossier is the same edition as that submitted by the ASMF holder, when completing Module 1.2 Application Form Section 2.5.3 and Annex 6.10.

Certificates of Suitability
When the drug substance is subject to an EDQM Certificate of Suitability, the applicant should ensure that the certificate is the current edition when completing Module 1.2 Application Form Section 2.5.3 and Annex 6.10.

5. REFERENCES

1 Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/consol_2004/human_code.pdf

2 Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf

3 Notice to Applicants Volume 2B Presentation and format of the dossier Common Technical Document (CTD)
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/ctd_06-2006.pdf

4 Notice to Applicants Chapter 7 – General Information
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/vol2a_chap7_2007-07.pdf

5 Additional data requested for new applications in the Mutual recognition and Decentralised procedures July 2007.
http://www.hma.eu/uploads/media/validation_Additional_Data_NA_in_MRP_DCP.pdf

6 FAQ on the *Community aquis* and data exclusivity for the reference product
http://www.hma.eu/20.html#irfaq_2_4b8e8

7 Legal basis for generic applications when the indication(s) of the reference medicinal product differ between RMS/CMS(s)
http://www.hma.eu/210.html#irfaq_8_d91c8

8 Interpretation and member states recommendation for applications submitted according to Article 10 when the strength and/or the pharmaceutical form of the reference medicinal product differs between RMS/CMS(s)
http://www.hma.eu/uploads/media/rec_art10.pdf

9 Information to be submitted by the member state of the European reference medicinal product
http://www.hma.eu/uploads/media/ERP_information.pdf

10 CPMP/EWP/QWP/1401/98 "The Investigation of Bioavailability and bioequivalence
http://www.emea.europa.eu/pdfs/human/qwp/140198enfin.pdf

11 Notice to Applicants Volume 2A Chapter 1 – Marketing Authorisations
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/vol2a_chap1_2005-11.pdf

12 Informed Consent Applications in Mutual Recognition and Decentralised Procedures Recommendations
http://www.hma.eu/uploads/media/recinfo_app.pdf

13 Member States recommendation on the Cover Letter for new applications submitted through the MRP/DCP
http://www.hma.eu/uploads/media/cover_letter_new_applications.pdf

14 Template for the Cover Letter for new applications submitted through the MRP/DCP http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Templates/MA_Application/cover_letter_new_applications.dot

15 Recommendations on Multiple/Duplicate applications in Mutual Recognition and Decentralised Procedures
http://www.hma.eu/uploads/media/rec_multiapp.pdf

16 EMEA Inspections – Good Manufacturing Practice: Question and Answers on GMP Matters
http://www.emea.europa.eu/Inspections/GMPfaq.html

17 Report from CMD(h) meeting held on 18th and 19th September 2006.
http://www.hma.eu/uploads/media/060918.pdf

18 EMEA/MRA/22/03 Final "Mutual Recognition Agreements between the EU and the respective parties Australia, Canada, New Zealand, and Switzerland"
http://www.emea.europa.eu/Inspections/docs/0002203en.pdf