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CMDh Best Practise Guide on the compilation of the dossier for new applications submitted in Mutual Recognition & Decentralised procedures

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 MSs.

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 applicant should ensure that:

- the product will be regarded as a medicinal product in all Member States concerned and that it will not be regarded, for example, as a cosmetic, a food supplement, a medical device or a biocide;
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- the application including the Module 2 with the three Overall Summaries and Overviews on Module 3, 4 and 5 is up to date and in accordance with relevant legislation ¹;
- For MRP and RUP only: variations or renewals to the original authorisation have been authorised by the Reference Member State in advance of the initiation of the procedure;

The format and content of the dossier should comply with current regulatory and national requirements.^{2,3,4,5,6}

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. For reasons of transparency, it is recommended to include copies of MSs Scientific Advice in Annex 5.14 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 Directive 2001/83/EC² only identical dossiers should be submitted to each MS involved in MRP/DCPs. Any additional data, which is specific to and is requested by a MS^{4,5} should be placed in Module 1 under "Additional Data", cf. CMDh Best Practice Guide on the use of the electronic common technical document (eCTD) in the mutual recognition and decentralised procedures⁶.

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

Applications made under Article 10 of Directive 2001/83/EC should include a discussion of the choice of reference medicinal product, 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 acquis* (see also the CMDh website Questions & Answers, Generic Applications⁷).

With reference to sections 1.4.2 and 1.4.3 of the Application Form, the reference medicinal product which is or has been authorised for not less than 6/10 years in the EEA, and the reference medicinal product authorised in MSs where the application is made and where relevant the medicinal product to which bioequivalence has been demonstrated by appropriate bioavailability study/studies should fall under the same global marketing authorisation.

Furthermore, only *one* reference medicinal product from the "same" MAH according to Commission Communication (98/C 299/03) and NtA chapter 1⁸ can be used within one MRP/DCP. The clarification text in the application form section 1.4.2 and 1.4.3 should be consulted.

If the reference medicinal product is nationally authorised (NP, MRP or DCP) the length of the data protection period is:

- 6/10 years if the application for the reference medicinal product was submitted before 30 October 2005, except for HR where the length of the data protection is 8 years also for reference medicinal products where the application was submitted before 30 October 2005;
- 8 years if the application for the reference medicinal product was submitted after 30 October 2005;

If the reference medicinal product is centrally authorised (CP) the length of the data protection period is:

- 10 years if the application for the reference medicinal product was submitted before 20 November 2005;
- 8 years if the application for the reference medicinal product was submitted after 20 November 2005;

For applications referring to a centralised approved medicinal product the relevant data protection period is starting from the date of notification to the marketing authorisation holder, which is not necessarily the date of granting the marketing authorisation by the Commission.

Non-Harmonisation Issues

In the case where the reference medicinal product is authorised in the RMS and CMSs, but the Summary of Product Characteristics (SmPC) has not been harmonised across MSs (sections 4.1-5.3), the applicant should review the differences and highlight these to the RMS.

In the case where the indications for the reference medicinal product differ between those approved in the RMS and the CMS, the CMDh advice "*CMDh Position Paper on Processing of Generic Applications when the Generic has more Indications or Fewer Indications than the Reference Product in the CMS*"⁹ should be followed.

In the case where the reference medicinal product (as the global marketing authorisation) is authorised in the RMS and CMSs, but without harmonisation of the marketed product strengths or pharmaceutical forms, then Q/A 14 in "*CMDh Q&A - Generic Applications*"¹⁰ should be followed.

Article 10 allows the use of a European Reference Product (ERP), when the reference medicinal product has not been authorised in one or more MSs included in the procedure. In this case, the CMDh advice in "*CMDh Working Document - Information to be submitted by the Member State of the European reference medicinal product*"¹¹ should be followed.

Reference Products used in Bioequivalence or Therapeutic Equivalence Studies

The applicant should discuss and justify the reference 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 product used as reference product in the bioequivalence study should be part of the global marketing authorisation of the reference medicinal product (as defined in Article 6(1) second subparagraph of Directive 2001/83/EC) and it should be authorised in the EEA.

See also the CHMP "**Guideline on the Investigation of Bioequivalence**" ¹².

For applications submitted under Article 10(3) and supported by a therapeutic equivalence study, the reference product used in the therapeutic equivalence study should be part of the global marketing authorisation of the reference medicinal product (as defined in Article 6(1) second subparagraph of Directive 2001/83/EC) and it should be authorised in the EEA.

If results from 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 active 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/EC² have been applied and met, and that the criteria in Chapter 1 of NtA Volume 2A are satisfactorily addressed⁸.

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 ⁸.

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 5.6 ⁸, and authorised in the Member States concerned in the procedure. Further CMDh advice is provided in "*Informed Consent Applications in Mutual Recognition and Decentralised Procedures Recommendations*" ¹³ and a template is made available "*Template for letter of Access for an application under Article 10c of Directive 2001/83/EC ('informed consent' application)*" ¹⁴.

Applicants should though take into account any legislation that is in force after approval of the reference medicinal product.

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 CMDh "*Member States recommendations on the cover letter for new applications submitted through the MRP/DCP*" ¹⁵. A template for the cover letter is available on the

CMDh website ¹⁶. The information in the cover letter will be dependent 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 subsequently 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 4.3. For further published advice, see "*Recommendations on Multiple/Duplicate applications in Mutual Recognition and Decentralised Procedures*" ¹⁷.

4.2 Responsibility for the application

The responsible person for the submission in each MS should be the Applicant/Future MAH, or an alternative authorised by the Applicant/Future MAH, mentioned in the Application Form and supported by appropriate documentation provided in Annex 5.4 of the Application Form.

4.3 Transfer of Ownership

Change of the future MAH during the DCP/MRP procedure

It is possible to change the future MAHs during the DCP/MRP procedure. The change should be included in an official response document submitted during the procedure and the change can only be submitted on:

- Day 40 of an MRP;
- Day 106 and day 160 of the DCP.

A future MAH can be changed only once per MS during a MRP/DCP procedure.

The change should be supported by appropriate information in the Application Form, Annex 5.19 of the Application Form (if applicable), a summary of the Pharmacovigilance system (sPhVS) of the new future MAH in module 1.8.1, and any additional documents required by individual MSs should be provided separately to the MS.

Change of the future MAH during the national implementation phase (after day 90/210)

The applicant should discuss with the particular Member State whether or not a change of the future MAH can be handled as part of the national implementation phase.

If a transfer of ownership for the product is to take place in the national phase after finalisation of the procedure, the MAH should submit variation application(s) via MRP to update the sPhVS and, if relevant, the RMP, see "*CMDh Guidance Document for Submission of Summary of the Pharmacovigilance System*".

Any additional documents required by individual MSs should be provided.

4.4 Manufacturing Authorisations for DC Procedures and GMP certificates

Satisfactory manufacturing authorisations (annex 5.6 of the Application Form) and GMP certificates (annex 5.9 of the Application Form) are required on initial submission.

In the case of EU sites, if the manufacturing authorisation and/or the GMP certificate is 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. The CMDh has agreed that in exceptional cases it should be possible to validate an application provided the Applicant commits to submit the missing documentation as part of the D106 response.

In the case of non-EU sites, if the manufacturing authorisation and/or the GMP certificate is absent, it is the responsibility of the applicant to apply for a GMP inspection to the relevant NCA, which is the authority in whose territory the batch releaser is located. In case the NCA, for any reason is not able to carry out the inspection, this can be delegated to another EEA NCA¹⁸. The application for inspection should be sufficiently in advance of the MAA submission to ensure that the inspection is complete and the corresponding GMP certificate is available on initial submission. However, with a view to avoiding delays in the start of a decentralised procedure, the CMDh has agreed that in exceptional cases it should be possible to validate an application, where a GMP inspection of sites outside the EU has not yet been carried out. The GMP certificate has to be available for the restart of the procedure on Day 106¹⁹.

If there is a Mutual Recognition Agreement (MRA) in place between the countries where the site is located and the European Union, the results of GMP inspections carried out by the MRA partner authority are normally recognised by the EU authorities²⁰.

4.5 Fees

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 to relevant MSs.

4.6 Active 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 5.10.

The applicant should indicate in the Application Form and the Cover Letter if the ASMF used for the application is participating in the EU/ASMF worksharing procedure.

Certificates of Suitability (CEP)

When the active substance is the subject of 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 5.10.

Qualified Person Declaration

The QP Declaration in annex 5.22 of the Application Form should preferably be prepared in the template "*Qualified Person's declaration concerning GMP compliance of the active substance manufacture*" "*The QP declaration template*"²¹. In case the template is not used, the provided declaration should contain the same set of details as the template, including each site involved in the synthesis of the active substance and date of audit.

4.7 Good Clinical Practice

The applicant should ensure that clinical trials including bioequivalence or therapeutic equivalence studies are/were carried out in compliance with GCP both in the clinic and in the analytical laboratory.

For further published advice, see GCP Inspectors Working Group's "Reflection paper on advice to applicants/sponsors/CROs of bioequivalence studies" ²².

4.8 Potential similarity to an orphan medicinal product

Before submitting a MA application, the applicant is advised to check the Union register of orphan medicinal products, for information on medicinal products designated as orphan which are under market exclusivity protection.

Module 1.2 Application Form Section 1.2.1 and section 1.2.2 should be completed. The applicant will have to indicate in section 1.2.2 if any medicinal product has been designated as an orphan medicinal product for a condition relating to the therapeutic indication proposed in the application. EU Orphan Designation Number(s) for any medicinal product designated as an Orphan medicinal product for a condition relating to the indication proposed in the application should be listed.

If any of the designated orphan medicinal products has been granted a marketing authorisation in the Union, and a period of market exclusivity is in force, the applicant will have to provide a similarity report in Module 1.7.1. Applicants are reminded that there is a specific template to use for their preparation of Module 1.7.1, see <https://www.hma.eu/human-medicines/cmdh/procedural-guidance/application-for-ma.html>. The completed template should be submitted in PDF format in Module 1.7.1 and in Word format in the "working documents" folder.

If the product in the MA application is considered to be similar to any authorised orphan medicinal product, a justification for a derogation should be provided in Module 1.7.2.

The applicant is recommended to verify if there is any change during the procedure, i.e, if any relevant Orphan medicinal products are granted a marketing authorisation.

For further published advice, see European Commission's "Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity" ²³, and the "User Guide for the electronic Application Form for a Marketing Authorisation" ²⁴.

5. References

¹ Notice to Applicants Volume 2A Chapter 2 – Mutual recognition procedure and decentralised procedure (http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm);

² 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. (http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm);

³ Notice to Applicants Volume 2B Presentation and format of the dossier Common Technical Document (CTD) (http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm);

⁴ Requirements on submission (number and formats) for New Applications within MRP; DCP or National procedures; Languages to be used for Marketing Authorisation Application (MAA), Variations and

Renewals; Mock-ups, Specimens and Samples for new applications; Blue-box requirements (<http://www.hma.eu/91.html>);

⁵ Additional Data requested for New Applications in the Mutual Recognition and Decentralised Procedures (<http://www.hma.eu/91.html>);

⁶ CMDh Best Practice Guide on the use of eCTD in the Mutual Recognition and Decentralised procedures (<http://www.hma.eu/277.html>);

⁷ CMDh Questions & Answers, Generic Applications (<http://www.hma.eu/20.html>);

⁸ Notice to Applicants Volume 2A Chapter 1 – Marketing Authorisations (http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm);

⁹ CMDh Position Paper on Processing of Generic Applications when the Generic has more Indications or Fewer Indications than the Reference Product in the CMS (<http://www.hma.eu/211.html>);

¹⁰ CMDh Q&A - Generic Applications (<https://www.hma.eu/20.html>);

¹¹ Information to be submitted by the member state of the European reference medicinal product (<http://www.hma.eu/211.html>);

¹² CHMP Guideline on the Investigation of Bioequivalence (<https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-clinical-pharmacology-pharmacokinetics>);

¹³ Recommendations on Informed Consent Applications in Mutual Recognition and Decentralised Procedures Recommendations (<http://www.hma.eu/91.html>);

¹⁴ Template for letter of Access for an application under Article 10c of Directive 2001/83/EC ('informed consent' application) (<http://www.hma.eu/219.html>);

¹⁵ Member States recommendation on the Cover Letter for new applications submitted through the MRP/DCP (<http://www.hma.eu/91.html>);

¹⁶ Template for the Cover Letter for new applications submitted through the MRP/DCP (<http://www.hma.eu/219.html>);

¹⁷ Recommendations on Multiple/Duplicate applications in Mutual Recognition and Decentralised Procedures (<http://www.hma.eu/91.html>);

¹⁸ EMA Inspections – Good Manufacturing Practice: Question and Answers on GMP Matters, Inspection coordination (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca);

¹⁹ Report from CMDh meeting held on 18th and 19th September 2006 (<http://www.hma.eu/256.html>);

²⁰ EMA/MRA/22/03 Final "Mutual Recognition Agreements between the EU and the respective parties Australia, Canada, New Zealand, and Switzerland" (<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra>);

²¹ Qualified Person's declaration concerning GMP compliance of the active substance manufacture "The QP declaration template" EMA/334808/2014 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000354.jsp&mid=WC0b01ac0580028bfd);

²² Reflection paper on advice to applicants/sponsors/CROs of bioequivalence studies
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000136.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296c4)

²³ European Commission Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity
(http://ec.europa.eu/health/files/orphanmp/doc/c_2008_4077_en.pdf)

²⁴ User Guide for the electronic Application Form for a Marketing Authorisation.
(<http://www.hma.eu/91.html>)