

Best Practice Guide on the assessment report for Mutual Recognition and Decentralised Procedures

Table of contents

1. Introduction	2
2. Legal framework	2
2.1. In general	2
3. Purpose of the assessment reports	2
4. Quality assurance	3
5. Content of the assessment report.....	3
6. Assessment reports in MRP and DCP	4
6.1. Assessment Report in MRP	4
6.2. Assessment Reports in DCP	5
6.3. Preparations for the Public Assessment Report	5
6.4. Updated assessment reports for repeat use procedures.....	5
7. Special features with regard to the assessment report for generic or hybrid applications	6

1. Introduction

Art 28 of Dir 2001/83 EG provides for an assessment report (AR) which describes the assessment of the medicinal product and states the reasons for the conclusions. The purpose of this guideline is to describe the structure and requirements of the assessment reports used in Mutual Recognition Procedures (MRP) and Decentralised Procedures (DCP).

2. Legal framework

According to Article 28, 1st paragraph of Directive 2001/83/EC, as amended one Member State, acting as Reference Member State (RMS) shall prepare an assessment report on the medicinal product. The 2nd paragraph of this article describes the procedure and timelines for the assessment report in case the product has already received a marketing authorisation in one member state, i.e. the MRP, while the 3rd paragraph deals with these issues for products which do not have a marketing authorisation in Europe at time of application, i.e. the DCP. In the 4th and 5th paragraphs the important role of the assessment report of the RMS during the procedures is explained, stating that the Member States concerned shall approve the assessment report and shall adopt the decision amongst others in conformity with the assessment report:

2.1. In general

This document should be read in conjunction with the following guidelines, Best Practice Guides and Standard Operating Procedures:

- Best Practice Guide for the decentralised and Mutual Recognition Procedure;
- Best Practice Guide for the Reference Member State in the MRP/DCP;
- Decentralised Procedure Member States' Standard Operating Procedure;
- Procedural Advice on Repeat Use;
- CMDh Best Practice Guide for the Public Assessment Report and Summary Public Assessment Report in MRP/DCP;

3. Purpose of the assessment reports

The assessment reports in the MRP and DCP are the key documents explaining why a marketing authorisation and each of the proposed indications have been or can be approved or rejected by the RMS and detailing the benefit-risk assessment for the product. It also serves as an audit trail explaining why an authorisation has been proposed, granted, or rejected and explaining the terms of the summary of product characteristics (SmPC), package leaflet (PL) and label. The reports should be sufficiently detailed to allow for secondary assessment by other Member States experts. As such these reports are central to the efficient operation of the mutual recognition procedure and the decentralised procedure.

An explanation of, and justification for each part of the SmPC, PL and label should be made referring to the relevant supporting data in the dossier.

Where it is recommended that a marketing authorisation to be granted is subject to conditions, these should be set out, clearly indicating the rationale and the timetable for receipt of results necessary to fulfil the additional requirements.

4. Quality assurance

The AR ought to be subject to a quality assurance programme within the RMS and the recommendations should be endorsed as representing the final opinion of the RMS.

5. Content of the assessment report

In general, there are five parts of the assessment report in MRP and DCP:

- Overview
- Quality
- Active Substance Master File (ASMF)
- Non clinical data
- Clinical data

For generic products it is possible to combine the non-clinical and clinical parts in one report and a separate template is available.

The Overview part will be the basis for the Public Assessment Report and has the following Index of Contents

Cover page	
I	Recommendations
II	Executive summary
II.1	Problem statement
II.2	About the product
II.3	General comments on the submitted dossier
II.4	General comments on compliance with GMP, GLP, GCP and agreed ethical principles
III	Scientific overview and discussion
III.1	Quality aspects
III.2	Non clinical aspects
III.3	Clinical aspects
IV	Benefit Risk Assessment
V	List of questions as proposed by the RMS*
VI	Recommended conditions for marketing authorisation and product information
VI.1	Conditions for marketing authorisation
VI.2	Summary of Product Characteristics (SmPC)
VI.3	Package Leaflet and User Testing (PL)
VI.4	Labelling
VII	Appendix: QRD guidance and checklist for the review of user testing results

* *This chapter is not applicable for the AR in the MRP*

Bioequivalence data

A confidential attachment (not to be disclosed to the applicant) should state the full composition of and specification for the reference product used in the bioequivalence studies in other Member States to enable the concerned Member States to compare it with that of the approved products marketed in their own countries.

ASMF

The overall content of the ASMF should contain detailed information as indicated under the various headings of the relevant Notice to Applicants for Marketing Authorisations for Medicinal Products in the Member States of the European Union, CTD format, section 3.2.S.

The applicant must be supplied by the ASMF holder with sufficient information to be able to take responsibility for an evaluation of the suitability of the active substance specifications to control the quality of the substance in the specified medicinal product. This information needs to be present in the Applicants part of the ASMF, which is to be submitted by the ASMF holder to both the applicant and the competent authorities/EMA. Detailed information on the individual steps of the manufacturing method such as reaction conditions, temperature, validation and evaluation data for certain critical steps of the manufacturing method etc. and on quality control during manufacture may contain valuable know how. Such information may be present in the closed part, which is to be submitted to the competent authorities/EMA only. In case the ASMF Worksharing Procedure is followed, reference is made to the CMDh Guidance on the worksharing procedure for the assessment of Active Substance Master File.

6. Assessment reports in MRP and DCP

The templates for the assessment reports in the MRP and DCP are published on the CMDh-website.

Further guidance with regard to the Overview in MRP and Overview and List of Questions in the DCP can be found in the concerned AR templates, in which further guidance is given on what kind of information is expected under the different headings.

For further guidance on the Quality, Non-clinical and Clinical parts reference is made to the Day 80 Guidance documents aimed to be used for the initial assessment of any new drug application in the centralised procedure. As the format of the CTD dossiers is the same in centralised, decentralised and mutual recognition procedure the same guidance can be used. There is a separate guidance available for the combined report on Module 4 and 5 for generic products. This guidance can be used for MRP as well as DCP.

6.1. Assessment Report in MRP

Before the start of a Mutual Recognition Procedure, the final decision on an application in the RMS takes place after several stages in the national authorisation procedure. At each stage of the assessment, a national draft-AR or pre-AR will be generated, and subsequently amended and updated in the light of new information from the applicant. By this iterative process the national pre- or draft-reports lead to the production of the AR, which will be the document exchanged between Member States in the mutual recognition procedure. For the national draft-AR or pre-AR it is highly recommended to start with the day 70 DCP templates. This structure will facilitate the drafting of the AR for the MRP.

The Quality part of the AR used in the MRP should be based on the updated, integrated dossier. The assessment of non-clinical and clinical parts of the AR may either be an integrated document reflecting the final position of the RMS or it will be produced from the submission as first made with clear

indications how this has been augmented by responses to objections. However the CMDh expressed a preference for an integrated report for the non-clinical and clinical parts.

If applicable, the (Overview) AR will also include a similarity assessment (Module 1.7.1). If necessary, a separate Similarity Assessment Report can be written. If applicable, an assessment of the claimed derogation(s) from orphan market exclusivity (Module 1.7.2) will be included in the Overview AR or in a separate AR on the derogation(s).

6.2. Assessment Reports in DCP

In the Decentralised Procedure, the RMS will generate a Preliminary Assessment Report (PrAR) and subsequently a Draft Assessment Report (DAR), which are the basis for decision making process between Member States. Separate AR templates are available for the day 70 (PrAR) and day 120 (DAR) Overview AR. The Overview part of the DAR is an update of the Overview part of the PrAR in which new information from the applicant submitted with the response document and conclusions from the RMS thereof have to be processed.

6.3. Preparations for the Public Assessment Report

The Best Practice Guide for the Public Assessment Report has highlighted the need for a Final Assessment Report, which forms the basis for the Public Assessment Report. The RMS will compile a final assessment report for all procedures. This consists of the Overview Part of the AR in case of MRP and an update of the DAR in case of DCP in which the scientific discussions between Member States and the final conclusions are reflected. If applicable, a short description of the discussion in break-out sessions and CMDh is included. The final SmPC, PL and label are attached.

This report forms the basis of the PAR and should therefore be finalised as soon as possible after the finalisation of the procedure. The report will be released to the applicant.

6.4. Updated assessment reports for repeat use procedures

Before the start of a repeat use procedure, there is a need for updating of assessment reports from MRPs and DCPs. Such a report could also form the basis for dealing with requests for MRP assessment reports from other regulatory authorities. The CMDh template for the Update Assessment report for Repeat Use Procedures can be used.

The following documents should be attached:

1. the initial assessment reports (AR in MRP; PrAR and DAR in DCP)
2. minutes of the break out session if held
3. minutes of the CMDh meeting during referral procedure if held
4. a note of any withdrawals and the reasons for the withdrawal
5. A copy of the approved specification for the active substance(s) and copies of the approved release and shelf-life specifications for the finished product or a statement that no changes to the original were necessary.
6. The (updated) similarity AR, if applicable.
7. The Final Assessment Report, including the agreed SmPC, PL and label

The updated assessment report should be accompanied by a chronology to take account of any subsequent variations, renewals, PSURs (if applicable), post approval commitments, Article 61(3) notifications and other procedures/information (for example variation/renewal assessment reports, decisions or notifications) to ensure that the updated mutual recognition assessment report is current as issued.

Note: For type IA and IB variations, reference is made to CTS. Only type II variations are listed.

If the medicinal product has been the subject of a referral to the CHMP which is finalised, the Commission decision and background scientific information should be included but it will not be necessary to include the assessment reports of the rapporteur/co-rapporteur.

6.5 Procedural overview

Phase	Time in procedure (days)	Report	Parts of the report	Content
MRP/RUP				
Start	-14 d	AR	AR-Overview AR-Module 3 AR-Module 4* AR-Module 5*	- Overview with summary of scientific discussion, recommendations. The SmPC, PL and label are attached. - Scientific discussion Module 3, 4 and 5.

* for generics, these parts can be combined

DCP				
Assessment step 1	70	PrAR	PrAR-Overview PrAR-Module 3 PrAR-Module 4 * PrAR-Module 5 *	- Overview with summary of scientific discussion, recommendations, List of Questions. The SmPC, PL and label are attached with comments included. - Scientific discussion Module 3, 4 and 5.
Assessment step 2	120	DAR	DAR-Overview DAR-Module 3 DAR-Module 4 * DAR-Module 5 *	- Update of the Overview of the PrAR with summary of scientific discussion, recommendations, List of Outstanding Issues. The SmPC, PL and label are attached with comments included. - Assessment of applicant's responses on Module 3, 4 and 5.
End of procedure	At latest day 210	FAR	FAR-Overview	- Overview with summary of scientific discussion, recommendations and, if applicable, a short summary of discussion in breakout-session and/or CMDh. The final SmPC, PL and label are attached.

* for generics, these parts can be combined

7. Special features with regard to the assessment report for generic or hybrid applications

Directive 2001/83/EC, as amended precisely stipulates the cases where the results of pharmacological and toxicological tests or clinical trials do not have to be provided, thus allowing for a generic, or a 'hybrid' application to be made. See also NTA Vol 2A Chapter 1, section 5 and 6 for detailed information concerning, data protection and bridging data in the case of hybrid applications under Art 10 (3) of Dir 2001/83/EC.

If the SmPC is different from that of the original product, the assessment report should outline the data supporting the modifications. In particular, if the RMS granted more indications for the reference product than the CMS, information on the underlying documentation for this additional indication should be given

In case of European Reference Product (ERP) and the information provided in the SmPC of the ERP (e.g. indications, contraindications, warnings) is different or even unknown in the RMS, a scientific dialogue should be initiated with the member state of the ERP to try to support the SmPC with data.

Where the SmPC and/or PL of the brand leader has been approved by a Commission Decision after a Referral based on Art 30 of Dir 2001/83 these SmPC and/or PL should be used for products with the same active substance and pharmaceutical form, unless justified.

For generic and hybrid applications the usual templates for the Overview and Quality parts of the AR can be used, but there is a separate, combined template for Module 4 and 5. It was agreed between the Member States that only bioequivalence and new data should be discussed in this part of the AR.