

The Common Technical Document (CTD)

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Ufficio Assessment Europeo

Catania – 10 Maggio 2014



Agenzia Italiana del Farmaco
AIFA

Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

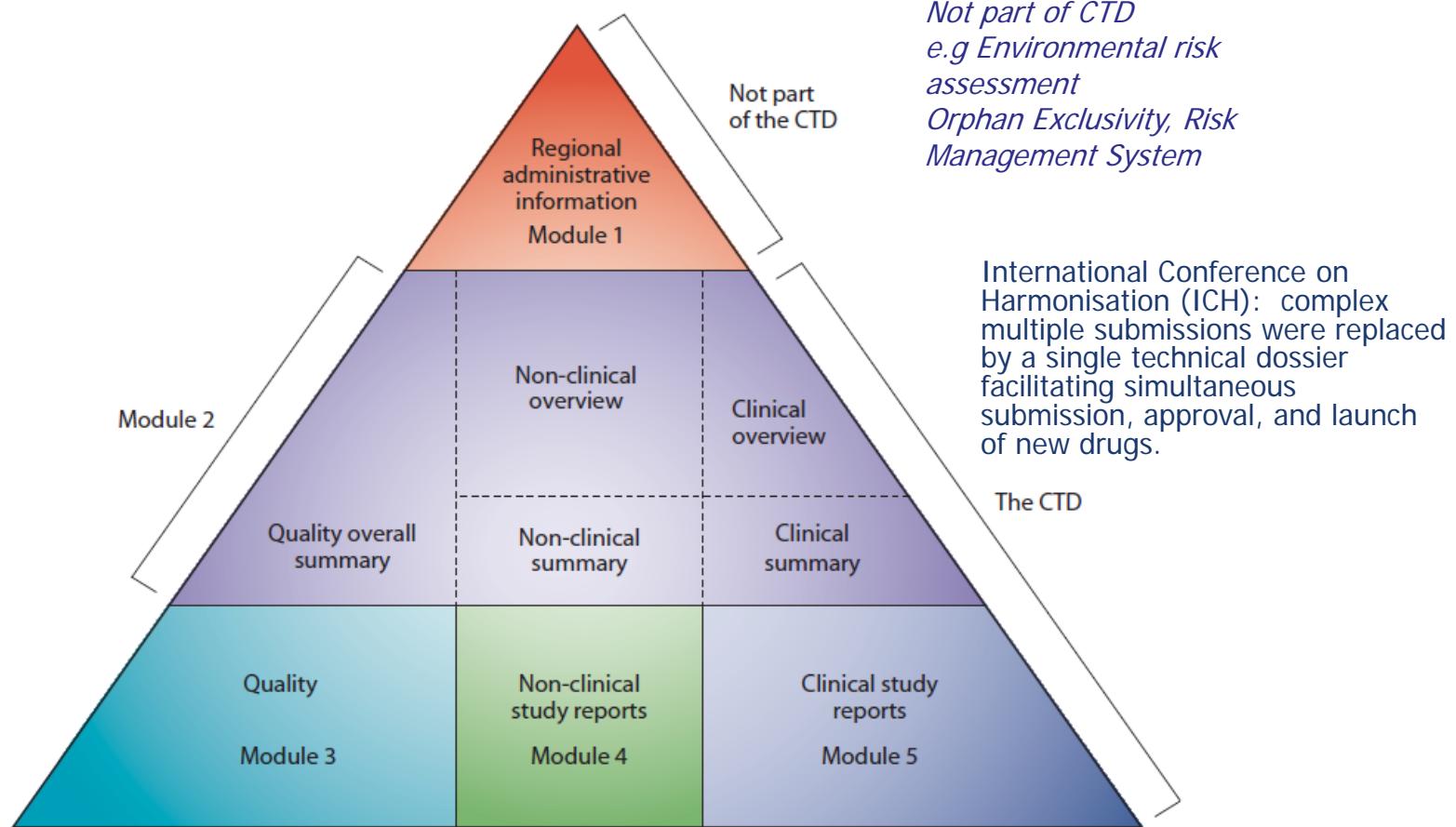
Interessi nell'industria farmaceutica	NO	Attualmente	Precedenti 2 anni	Da oltre 2 a 5 anni precedenti	Oltre 5 anni precedenti (facoltativo)
Interessi diretti:					
Impiego in una società	X				
Consulenza per una società	X				
Consulente strategico per una società	X				
Interessi finanziari	X				
Titolarità di un brevetto	X				
Interessi indiretti:					
Sperimentatore principale	X				
Sperimentatore	X				
Sovvenzioni o altri fondi finanziari	X				

* Alessandra Tamburella, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 26.01.2012 e pubblicato sulla Gazzetta Ufficiale del 20.03.2012 in accordo con la policy 0044 EMA/513078/2010 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. < Il compenso ricevuto per questo intervento è regolato dalla contrattazione collettiva>.



Common Technical Document since 1996



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.



COMMISSION DIRECTIVE 2003/63/EC

- *The detailed scientific and technical requirements of Annex I to Directive 2001/83/EC need to be adapted to take account of scientific and technical progress and in particular of a large set of new requirements resulting from recent legislation. The presentation and content of the marketing authorisation application dossier have to be improved in order to facilitate the assessment and the better use of certain parts of the dossier which are common to several medicinal products.*



eCTD

From 1 January 2010, eCTD is the only acceptable electronic format for all applications and all submission types in the context of the centralised procedure (e.g. new applications, variations, renewals).

ICH M2 eCTD specification:
<http://www.ich.org/products/electronic-standards.html>

eCTD EU Module 1 specification: Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2B



Validation

- Initial marketing authorisation (MA) applications submitted to the European Medicines Agency (EMA) as part of the centralised procedure are subject to a validation process.
- After receiving the confirmation of technically valid submission through the Gateway or the Web Client from the Agency, the applicants must submit the application to all (Co-)Rapporteurs (otherwise: delay)



All Dossiers - ETRS is Yours - The European Review System - [SOVRiad\SOVRiad...\Application Form]

Submission-Explorer Country Filter: EMEA

1.0 Cover letter
 1.2 Application form
 1.3 Product Information
 1.4 Information about the Experts
 1.5 Specific Requirements for Different Types of Applications
 1.6 Environmental Risk Assessment
 1.7 Information relating to Orphan Market Exclusivity
 1.8 Information relating to Pharmacovigilance
 1.9 Information relating to Clinical Trials
 1.10 Information relating to Pediatrics
 Additional Data
 Responses to Questions

2 Common Technical Document Summaries
 2.2 Introduction
 2.3 Quality Overall Summary
 2.3 Introduction
 2.3.5 Drug Substance - Simeprevir - All
 2.3.5 Drug Product - All - Active - Capsule
 2.3.A Appendices
 2.3.R Regional Information
 2.4 Nonclinical Overview
 2.5 Clinical Overview
 2.6 Nonclinical Written and Tabulated Summaries
 2.6.1 Introduction
 2.6.2 Pharmacology Written Summary
 2.6.3 Pharmacology Tabulated Summary
 2.6.4 Pharmacokinetics Written Summary
 2.6.5 Pharmacokinetics Tabulated Summary
 2.6.6 Toxicology Written Summary
 2.6.7 Toxicology Tabulated Summary
 2.7 Clinical Summary
 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
 2.7.2 Summary of Clinical Pharmacology Studies
 2.7.3 Summary of Clinical Efficacy - chronic Hepatitis C
 2.7.4 Summary of Clinical Safety
 2.7.5 Literature References
 2.7.6 Synopses of Individual Studies

3 Quality
 3.2 Body of Data
 3.2.5 Drug Substance - Simeprevir - All
 3.2.5 Drug Product (Active, Capsule) - All
 3.2.A Appendices
 3.2.R Regional Information
 3.3 Literature References

4 Nonclinical Study Reports
 4.2 Study Reports
 4.3 Literature References

5 Clinical Study Reports
 5.2 Tabular Listing of all Clinical Studies
 5.3 Clinical Study Reports
 5.4 Literature References

Attributes Annotations 1 / 35 136% Strumenti Firma Commento

EUROPEAN COMMISSION
 ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
 Consumer goods
 Pharmaceuticals

Brussels,
 F2/ (2008)

Revision 9

NOTICE TO APPLICANTS

Medicinal Products for Human Use

VOLUME 2B
Module 1: Administrative information
Application form

May 2008

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Module 1

-  1.0 Cover letter
-  1.2 Application form
-  1.3 Product Information
-  1.4 Information about the Experts
-  1.5 Specific Requirements for Different Types of Applications
-  1.6 Environmental Risk Assessment
-  1.7 Information relating to Orphan Market Exclusivity
-  1.8 Information relating to Pharmacovigilance
-  1.9 Information relating to Clinical Trials
-  1.10 Information relating to Paediatrics
-  Additional Data
-  Responses to Questions

[1](#) [2](#) Common Technical Document Summaries



Module 1

Module 1 - Administrative information and prescribing information

- The cover letter to the application should be included here.
- Where necessary, a “Notes to Reviewers” document could be provided as an Appendix to the cover letter
- 1.2 Application form
- Module 1.2 is to be used for an application for a marketing authorisation of a medicinal product for human use submitted to
- (a) the EMA under the centralised procedure or
- (b) a Member State (as well as Iceland, Liechtenstein and Norway) under either a national, mutual recognition or decentralised procedure.



Module 1

- 1.3 Product Information
- In accordance with Article 8.3 (j), Article 11 and Title V of Directive 2001/83/EC
- 1.3.1 SPC, Labelling and Package Leaflet
- 1.3.2 Mock-up Directive 2001/83/EC Article 8
- Module 1.3.3 Specimen Title V of Directive 2001/83/EC (e.g. Article 56).
- 1.3.4 Consultation with Target Patient Groups - Articles 59(3) and 61(1) of Directive 2001/83/EC
- Module 1.3.6 Braille Article 56a of Directive 2001/83/EC



Module 1

- 1.4 Information about the Experts Article 12 of Directive 2001/83/EC
- In accordance with experts must provide detailed reports of the documents and particulars which constitute Modules 3, 4 and 5.
- 1.5 Specific requirements for Different Types of Applications
- 1.5.1 Information for Bibliographical Applications Article 10a of Directive 2001/83/EC
- 1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications
For applications based upon Article 10(1), 10(3) or 10(4) of Directive 2001/83/EC



Module 1

- 1.5.3 (Extended) Data / Market Exclusivity

The 10- year period of marketing protection may be extended by one year for new therapeutic indications (Article 10(1) of Directive 2001/83/EC and Article 14(11) of Regulation 726/2004)

A non-cumulative period of one year of data exclusivity may be granted for a new indication for a well-established substance (Article 10(5) of Directive 2001/83/EC)

Where a change of classification of a medicinal product has been authorised (Article 74a of Directive 2001/83/EC)

- 1.5.4 Exceptional circumstances (Article 22 of Directive 2001/83/EC and Article 14(7) of Regulation (EC) No 726/2004)
- 1.5.5 Conditional marketing authorisation (Article 14(7) of Regulation (EC) No 726/2004)



Module 1

- 1.6 Environmental Risk Assessment (ERA) (Article 8 (ca) and (g) of Directive 2001/83/EC)
- 1.7 Information relating to Orphan Market Exclusivity
- 1.7.1 Similarity
- 1.7.2 Market Exclusivity

This section is required for all new Applications (not only for Designated Orphan medicinal products) as well as for Type II variations for new indications, where the indication applied for is the same as the indication of an authorised Orphan Medicinal Product (Article 8.1 of Regulation (EC) No 141/2000)



Module 1

- 1.8 Information relating to Pharmacovigilance
- 1.8.1 Pharmacovigilance System
- According to Article 8 (ia) of Directive 2001/83/EC
- 1.8.2 Risk-management System
- According to Article 8 (ia) of Directive 2001/83/EC a detailed description of the riskmanagement system which the applicant will introduce should be provided, where appropriate.
- The detailed description of a risk management system should be provided in the form of an EU Risk Management Plan (EU-RMP) Volume 9A of Eudralex (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/home_v9.htm).



Module 1

- 1.9 Information relating to Clinical Trials
- According to Article 8 (ib) of Directive 2001/83/EC a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC should be provided, where applicable
- This statement should indicate that “clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC” together with a listing of all trials (protocol number) and third countries involved



Module 1

- 1.10 Information relating to Paediatrics
- With reference to Article 7, 8 and 30 of Regulation (EC) No 1901/2006 ('paediatric regulation'), this section is required:
- as of 26 July 2008 for all new Applications* for a medicinal product which is not authorised in the EEA
- as of 26 January 2009 for applications* for new indications, new pharmaceutical forms and new routes of administration, for authorised medicinal products which are protected either by a supplementary protection certificate, or by a patent which qualifies for the granting of such a certificate
- for Paediatric Use marketing authorisation applications (PUMA)



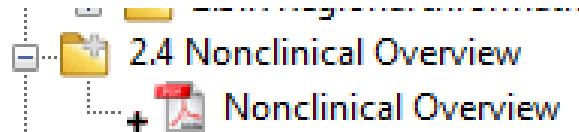
Module 2



- [Module 2.2 Introduction](#)
- The general introduction to the medicinal product should include its pharmacological class, mode of action and the proposed clinical use. In general the introduction should not exceed one page.
- [Module 2.3 Quality Overall Summary](#)
- The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.



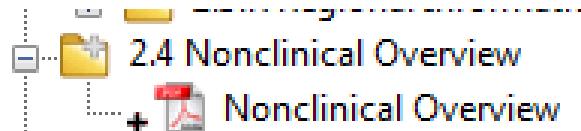
Module 2.4 Nonclinical Overview



- The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document.
- It should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical.
- The nonclinical testing strategy should be discussed and justified. There should be comment on the GLP status of the studies submitted.
- Relevant scientific literature and the properties of related products should be taken into account.



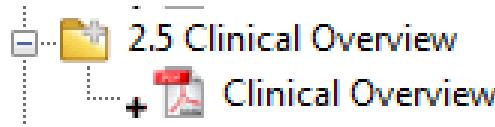
Module 2.4 Nonclinical Overview



- The Nonclinical Overview should be presented in the following sequence:
- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature references



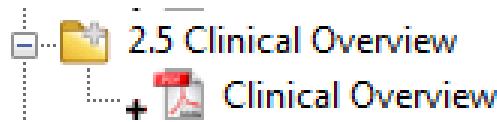
Module 2.5 Clinical Overview



- The Clinical Overview is intended to provide a critical analysis of the clinical data in the CTD.
- Is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application.
- Should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.



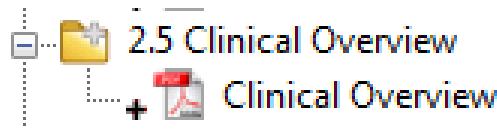
Module 2.5 Clinical Overview



- Describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions;
- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance;
- provide a brief overview of the clinical findings, including important limitations;
- provide an evaluation of benefits and risks
- address particular efficacy or safety issues;
- explore unresolved issues;
- explain the basis for important or unusual aspects of the prescribing information.



Module 2.5 Clinical Overview



- 2.5.1 Product Development Rationale
- 2.5.2 Overview of Biopharmaceutics
- 2.5.3 Overview of Clinical Pharmacology
- 2.5.4 Overview of Efficacy
- 2.5.5 Overview of Safety
- 2.5.6 Benefits and Risks Conclusions
- 2.5.7 Literature References



2.6 Nonclinical Summaries

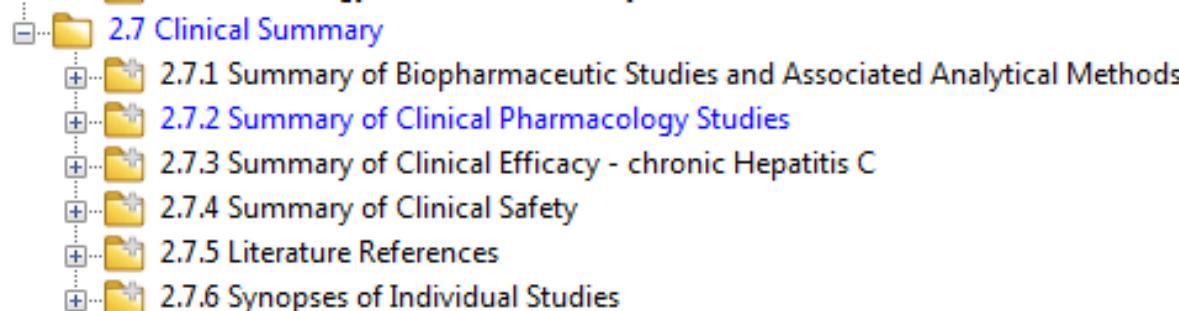
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 - 2.6.7 Toxicology Tabulated Summary

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.



Module 2.7 Clinical Summary

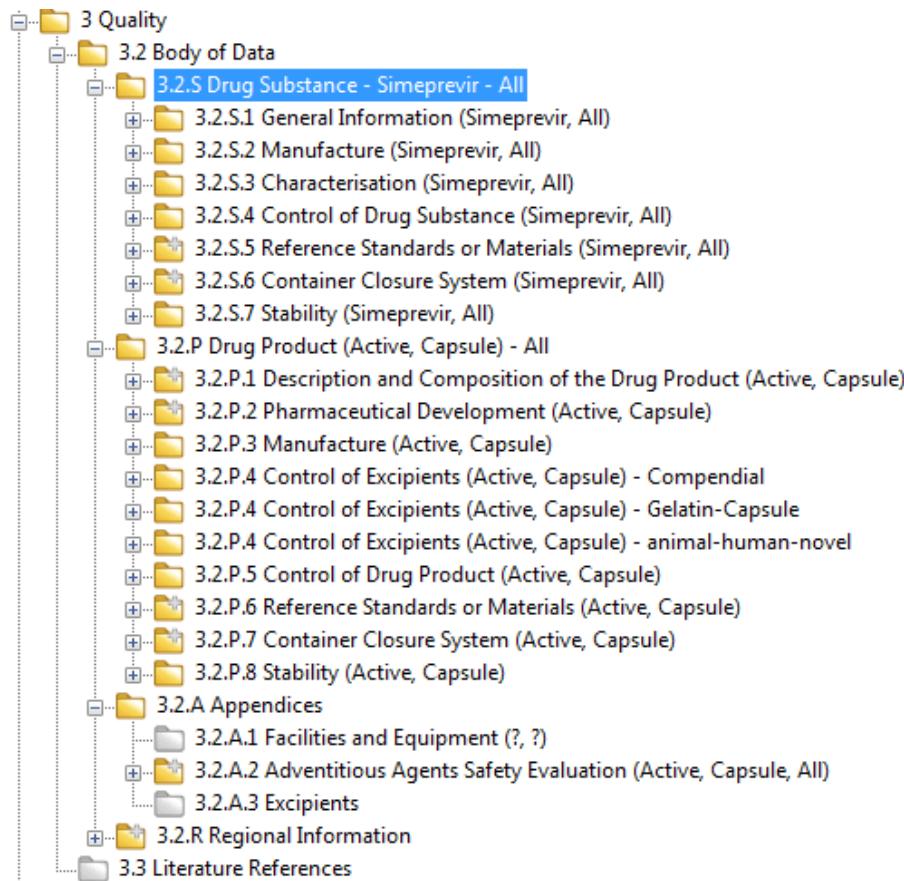


The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the Common Technical Document.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.



Module 3 - Quality



Principle of GMP and the detailed guidelines (Article 40 of Directive 2001/83/EC as modified)

Relevant also for all other large scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, for the preparation of products for use in clinical trials, and for wholesaling, were applicable.

All analytical test procedures described in the various sections of the chemical, pharmaceutical and biological documentation must be described. All procedures need to be validated and the results of the validation studies must be provided.



Module 4



Module 5

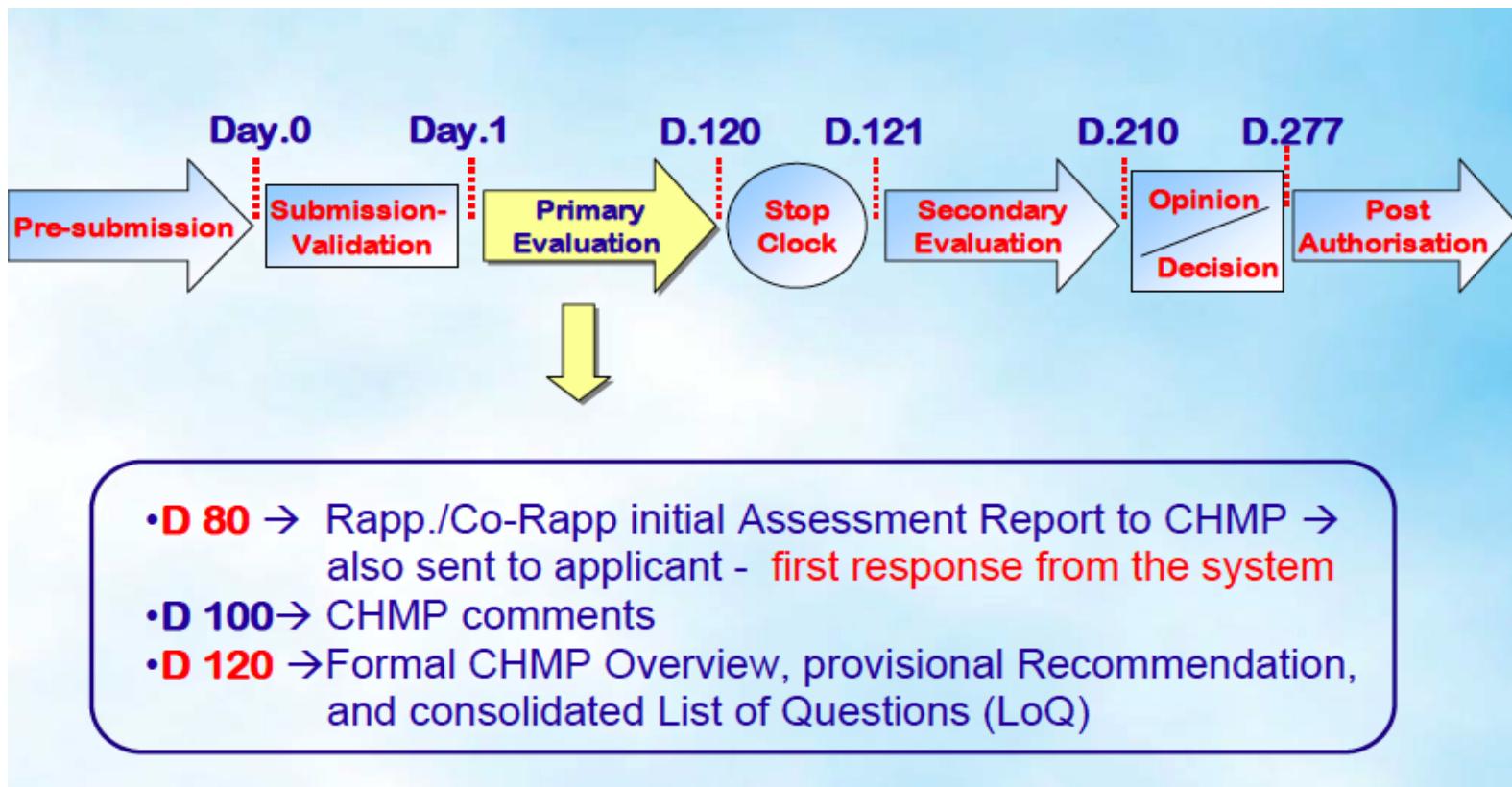
- 5 Clinical Study Reports
 - 5.2 Tabular Listing of all Clinical Studies
 - + Tabular Listing of all Clinical Studies
 - 5.3 Clinical Study Reports
 - 5.3.1 Reports of Biopharmaceutic Studies
 - + 5.3.1.1 Bioavailability (BA) Study Reports
 - + 5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports
 - 5.3.1.3 In vitro - In vivo Correlation Study Reports
 - + 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies
 - 5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
 - + 5.3.2.1 Plasma Protein Binding Study Reports
 - + 5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies
 - + 5.3.2.3 Reports of Studies Using Other Human Biomaterials
 - 5.3.3 Reports of Human Pharmacokinetic (PK) Studies
 - + 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports
 - + 5.3.3.2 Patient PK and Initial Tolerability Study Reports
 - + 5.3.3.3 Intrinsic Factor PK Study Reports
 - + 5.3.3.4 Extrinsic Factor PK Study Reports
 - + 5.3.3.5 Population PK Study Reports
 - 5.3.4 Reports of Human Pharmacodynamic (PD) Studies
 - + 5.3.4.1 Healthy Subject PD and PK/PD Study Reports
 - + 5.3.4.2 Patient PD and PK/PD Study Reports
 - 5.3.5 Reports of Efficacy and Safety Studies - chronic Hepatitis C
 - + 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
 - + 5.3.5.2 Study Reports of Uncontrolled Clinical Studies
 - + 5.3.5.3 Reports of Analyses of Data from More than One Study
 - + 5.3.5.4 Other Study Reports
 - 5.3.6 Reports of Postmarketing Experience
 - 5.3.7 Case Report Forms and Individual Patient Listings
 - + 5.4 Literature References



The (Co-)Rapp D80 Assessment Reports Peer Review: a tool for the Quality Assurance of the D120 List of Questions



D80 (Co-)Rapp AR – Peer Review



Peer Review

- The overall aim of the Peer Review is to contribute to the quality assurance of the LoQ intended for the applicant by reviewing the proposed questions in conjunction with the scientific reasoning made by the (Co) Rapporteurs in their initial assessment reports.
- 2 main aspects:
- 1. The extent to which the scientific argumentation in the (Co) rapporteurs' assessment reports supports the proposed questions in the LoQ;
- 2. The consistency between issues raised in the Day 120 LoQ and the CHMP guidelines/Scientific Advice and issues raised in the assessment of products within the same class/same indication.



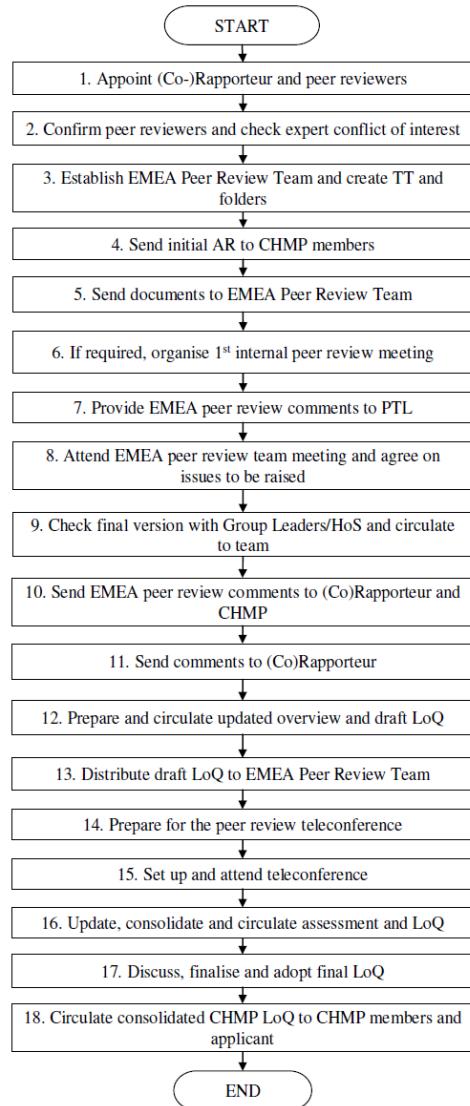
However, in order to be able to address those two main aspects, particularly in the context of different views expressed by the two rapporteurs and/or by other CHMP members, the peer reviewer also needs to confirm or not that the initial assessment reports describe different topics in sufficient detail to allow secondary assessment (in practice this means that the (Co) Rapporteur's assessment reports should fulfil criteria set out in template and guidance documents adopted by the CHMP

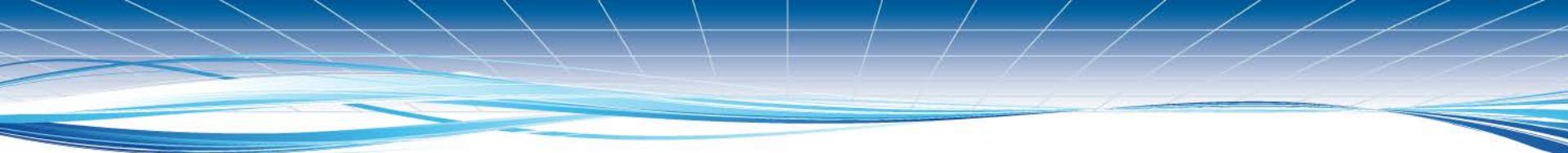


- The peer review/QA exercise is based on the different modules – Quality, Non-Clinical, Clinical and Overview/LoQ of the (Co)Rapporteurs' initial assessment reports which should be sufficiently readable, detailed (and self-explanatory) to allow the peer reviewer to critically assess pivotal data without having to read the original application dossier.
- The Peer Reviewers shall have access to the overview/expert report (module 2 of the application). Peer review comments are most useful when they are both critical and constructive, proposing specific changes to the assessment and the LoQ!
- The Rapporteurs remain responsible for the content of the different parts of the assessment reports and the proposed "Overview and LoQ" and will consider what changes to be considered for inclusion in the documents.



PR Flow Chart





Thanks again for your attention!!

Any questions?

CONTATTI

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