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QUALITY STANDARDS AND GUIDANCES. OVERVIEW RELATED TO THE MAIN REGULATORY AUTHORITIES

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ACTIVE SUBSTANCE MASTER FILE

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WHAT IS AN ACTIVE SUBSTANCE MASTER FILE?

It is a document prepared by a manufacturer (holder) to provide the regulatory authority with confidential, detailed information about an Active Ingredient intended to be used in human or veterinary drugs products.

It can be called ACTIVE SUBSTANCE MASTER FILE (ASMF) or DRUG MASTER FILE (DMF), depending on regulatory requirements of the authority to which the document is submitted.

In Europe, it is commonly called ASMF, in Canada Type-I ASMF, in Australia and New Zealand DMF, in USA Type-II DMF.

The same document, called Dossier, it is submitted to the European Directorate for the Quality of Medicines to obtain the Certificate of Suitability.

Most of the regulatory agencies worldwide, even outside from ICH regions, accept documents similar to ASMF for API registration. In Italy it is filed also as part of documentation relevant to production authorisation/registration.

WHAT IS THE ACTIVE SUBSTANCE MASTER FILE USED FOR?

The evaluation by Regulatory Bodies of all the topics relevant to Active Ingredients is a very important part of the procedure for granting Marketing Authorisation to pharmaceutical products.

Typically, an ASMF is filed when the API Manufacturer is not the same company that manufactures the drug product or that applies for MA. The ASMF filing allows API Manufacturer to protect its intellectual property from its commercial partner while complying with regulatory requirements for disclosure of processing details.

In fact, ASMF comprises two parts: the Applicant's Part (or Open Part), which contains all the information that the MA holder needs to assess the quality and submit its application; and the Restricted Part (or Closed Part), which contains confidential information about the manufacturing procedure only disclosed to the authorities.

WHAT APIs CAN BE DESCRIBED IN THE ASMF?

An ASMF can be filed for:

- New Chemical Entities
- Known and well established APIs with or without a compendial monograph.

APIs from biological sources, blood and derivatives, vaccines are outside the scope of ASMFs, and different documents are required.

If an API is described in European Pharmacopoeia, the ASMF (called Dossier in this case) is part of the documentation needed to obtain CEP.

HOW ASMF IS REVIEWED AND EVALUATED?

ASMF is reviewed only in conjunction with a MAA (for human or veterinary drug products), in order to assess if the API is suitable for the intended use.

The ASMF holder should authorise the Authority to review the document as part of a specific application. Such an authorisation is given in written form by means of a «Letter of Access» or «Letter of Authorisation».

For this reason, ASMF is never approved or rejected as stand-alone document.
In case gaps in the content are found, the reviewer can ask to the API Manufacturer to provide missing information or further clarification and data.
If the request is relevant to Restricted Part, questions are sent directly to the ASMF holder, to preserve confidentiality

WHAT IS THE CONTENT OF AN ASMF?

The main information given in the ASMF are relevant to the product description, manufacturing process and control of raw materials, characterisation of the molecule, description of impurities, specifications and analytical methods, including description of method validation, description of packaging and stability data.

CONTENT OF AN ASMF – SELECTION OF API SM

"An API starting material is a raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API."
From API SM on, all manufacturing steps are subject to GMP requirements.

The selection of API SM for the manufacturing process of an API and its justification (including acceptance specification) is frequently one of the most crucial steps in an ASMF review, since the characteristics of this material can affect the impurity profile of the final product.

CONTENT OF AN ASMF – IMPURITIES AND THEIR LIMITS

A very thorough discussion about impurities potentially present is expected, taking into account the actual synthetic process.

In particular, details are needed about

- Related Compounds
- Residual Solvents
- Elemental impurities
- Genotoxic Impurities
- Different solid forms (e.g polymorphic forms)

Wherever necessary, suitable tests and limits should be set to control the potentially present impurities.

CONTENT OF AN ASMF – STABILITY AND STORAGE CONDITIONS

Results of stability studies performed following established protocols are expected.
Studies are performed at least on Accelerated and Long-term conditions established for Climatic Zones I and II.
Methods used to perform stability studies should be demonstrated to be stability-indicating (e.g. by forced degradation studies)
Depending on the submission country and zone, different studies could be required.

Based on the results of Stability Studies, the relevant Retest or Expiry date should be set. Such a date can be included in CEP at discretion of the holder.

WHAT IS THE FORMAT OF AN ASMF?

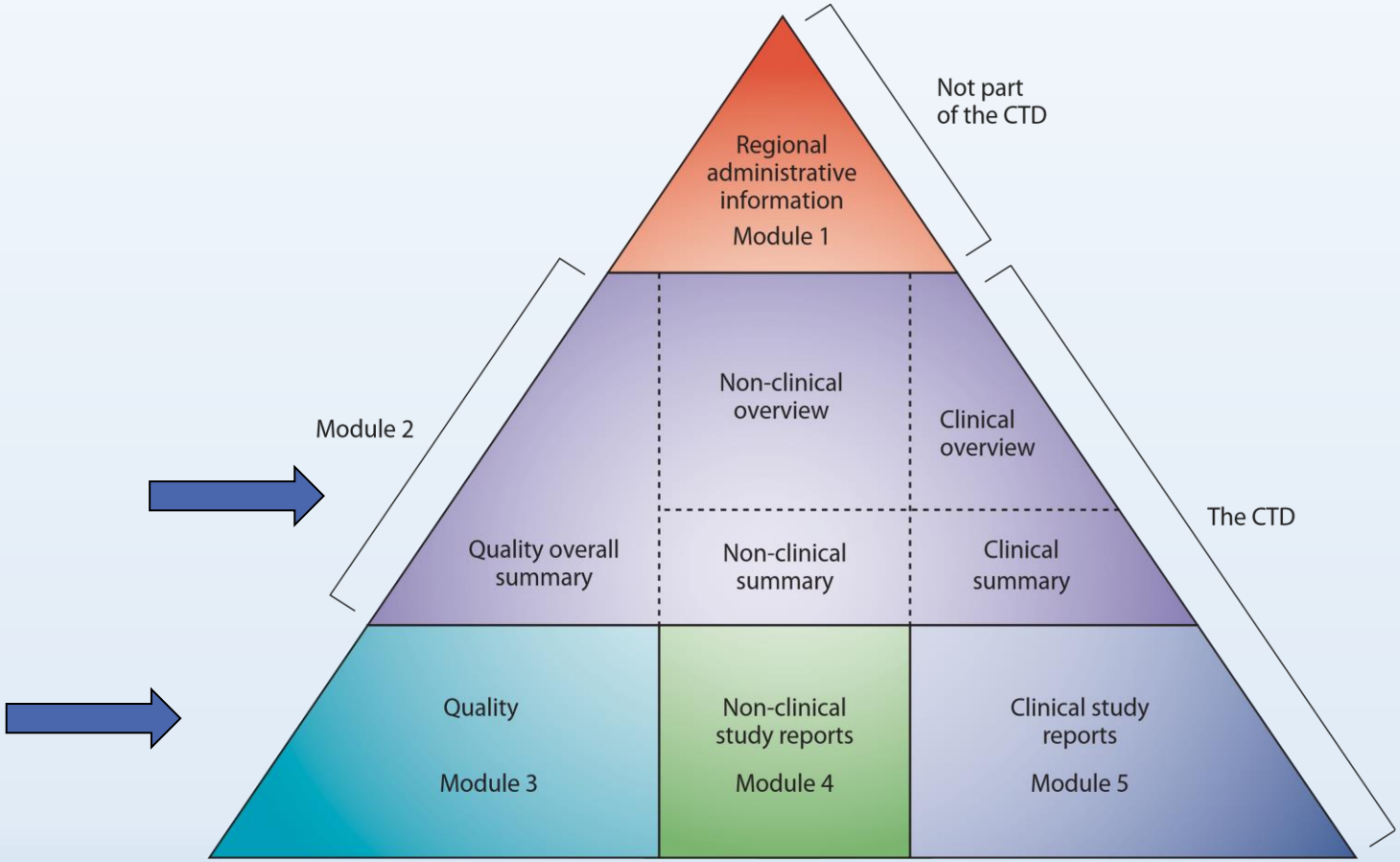
In the ICH regions, a common format has been established for the ASMF.
This format, called Common Technical Document, has been developed to harmonise documents and make review easier, since a standard table of contents has been set for Marketing Authorisation Application, of which ASMF is part.
During years, this documental format has been accepted also by non-ICH countries.

CTD is composed of fixed Modules, and the ones relevant to API are

- Module 2 – Quality Overall Summaries – Section 2.3.S
- Module 3 – Quality - Body of data – Section 3.2.S

The organisation of chapers and sub-chapters is fixed, and it is called «granularity».
The correct granularity is a pre-requisite for electronic submissions.

THE CTD TRIANGLE



CTD - THE TABLE OF CONTENT

SECTION	CONTENT
3.2.S.1	General information Nomenclature –Structure –General Properties
3.2.S.2	Manufacture Manufacturer(s) - Description of manufacture and In-Process controls – Control of materials – Control of critical steps and intermediates – Manufacturing Process Development
3.2.S.3	Characterisation Elucidation of structure - Impurities
3.2.S.4	Control of Drug Substance Specification – Analytical Procedures – Validation of Analytical Procedures – Batch Results – Justification of specification
3.2.S.5	Reference standards or materials
3.2.S.6	Container closure system
3.2.S.7	Stability Stability Summary and Conclusion – Post-approval stability protocol and commitment – Stability data

CHANGES TO ASMF

The holder has to maintain the ASMF current and updated.
The content should always reflect the actual process, so, in case of changes to manufacturing, testing , packaging or storage conditions, a new edition of the document should be prepared and submitted to authorities.
Moreover, customer will always be informed of the new edition.

In case the ASMF supports a CEP, EDQM will be notified of the update and, if applicable, a new CEP revision will be issued.

GUIDELINES AND REFERENCE DOCUMENTS

	ASMF PROCEDURE
WHO	Technical Report Series No 948, Annex 4 Guidelines on ASMF procedure
EMA	CHMP/QWP/227/02 Rev.03 Guideline on Active Substance Master File (con riferimenti agli Herbals) Eudralex – Vol. 1 /5
US-FDA	Guideline for Drug Master File
TGA	Guidance 11 – Drug Master Files and Certificate of Suitability
MedSAFE	Guideline on regulation of therapeutic products – Part 2
Health Canada	Guidance document: Master Files

	API STARTING MATERIAL
ICH	Q7
ICH	Q11 – Development and manufacture of Drug Substances
ICH	Q11 Q&A - Selection and justification of starting materials for the manufacturing of drug substances

	IMPURITIES
ICH	ICHQ3A(R2) Impurities in drug substances
EP	General monograph < Substances for pharmaceutical use
EP	General Chapter < Control of impurities in substances for pharmaceutical use
USP	<1086> Impurities in Drug substances and drug products
ICH	Q3C(R7) Guideline for Residual solvents
ICH	Q3D – Guideline for Elemental Impurities
ICH	Q6A – Specifications
ICH	M7 – Genotoxic Impurities
USFDA	ANDAs- Pharmaceutical Solid Polymorphism
EMA	CHMP/CVMP/QWP/199250 – Setting specifications for related impurities in antibiotics

	STABILITY
ICH	Q1A(R2) –Stability of drug substances
ICH	Q1B – Photostability testing of new active substances and medicinal products
WHO	Technical Series No 953, 2009, Annex 2 Stability testing of Active Pharmaceutical Ingredients
EMA	CPMP/QWP/609/96 Rev.02 - Guideline on declaration of storage conditions
	FORMAT
ICH	M4 – Common Technical Document
ICH	M4Q (R1) - Quality
ICH	M8 – Electronic Common Technical Document (eCTD)
	PA/PH/CEP (09) 108, 5R - Guidance for electronic submissions for Certificates of Suitability (CEP) applications

	CHANGES
EDQM	PA/PH/CEP (04), 2 Guideline on requirements for revision/renewal for Certificates of Suitability of European Pharmacopoeia
ICH	Q12 – Lifecycle Management (draft)
EMA	CHMP/QWP/227/02 Rev.03 Guideline on Active Substance Master File