UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI
SCIENZE FARMACEUTICHE
Sezione di Tecnologia e Legislazione Farmaceutiche Maria Edvige Sangalli

Corso di Laurea Magistrale in Chimica e Tecnologia Farmaceutiche – E25

Fabbricazione Industriale dei Medicinali – 4 CFU

Prof. Andrea Gazzaniga

Il Dossier di Registrazione

Dott. Attilio Sarzi Sartori – Chiesi Farmaceutici S.p.A.

gazza

Corso di laurea in Chimica e Tecnologia Farmaceutiche

Il Dossier di Registrazione

Attilio Sarzi Sartori
Chiesi Farmaceutici S.p.A.

DOSSIER

ANNEX I Directive 2001/83/EC
amended by Directive 2003/63/EC
ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS

AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

(in Italy it was implemented in the national legislation decree– G.U. 254 28/10/04 in force on 12/11/04)/D.Lgs 219 24/4/06

GUIDELINE "NOTICE TO APPLICANTS"
(edition 1998 - in force until 30/6/2003)

COMMON TECHNICAL DOCUMENT (CTD)
(edition 2003 – mandatory since 1/7/2003)
(update 5/2008)

Common Technical Document

Definizione: un formato comune concordato per le tutte le tipologie di procedure presentate nelle Tre Regioni (EU, US e J)

Obiettivi

- Un accesso più rapido dei nuovi farmaci sul mercato
- Eliminazione di ritardi inutili nello sviluppo di farmaci
- Eliminazione della duplicazione di studi su animali o sull'uomo (ottimizzazione delle risorse)
- Protezione della Salute Pubblica

Obiettivi

- Industria (Format comune per la documentazione tecnica)
  - Riduzione delle risorse necessarie per le varie procedure
  - Una più facile preparazione della submission elettronica

- Autorità Regolatorie (Documentazione standard)
  - Revisioni facilitate
  - Miglioramento delle interazioni con l'Applicant
  - Semplificazione nei passaggi di informazioni fra Agenzie Regolatorie

Ambito di applicazione

- Organizzazione dell'informazione da presentare in occasione di procedure di registrazione per nuove specialità medicinali (inclusi i prodotti bio-tecnologici)
- Applicabile anche per procedure abbreviate e variazioni
- Srettamente correlato alla definizione del solo format

NOTICE TO APPLICANT: Volume 2B

Presentation and content of the dossier – CTD 2008 edition

Notice to Applicants, Volume 2B – **Common Technical Document (CTD)**
(updated version May 2008)

Notice to Applicants , Volume 2B – Questions and Answers
(updated version May 2008)

DOSSIER

- Il Common Technical Document è il formato più aggiornato del dossier di registrazione

- Il CTD fu implemetato nel Luglio 2003.

- Il nuovo formato riguarda tutte le procedure di registrazione (MRP/DCP, Centralizzate, Nazionali compelte o abbreviate)

DOSSIER

- Implementazione delle linee guida internazionali, Farmacopea Europea , GxP etc.

- Inclusione di tutte le informazioni disponibili per consentire una corretta valutazione

- Aggiornamento continuo

- Inclusione di sezioni generali e sezioni speciali per specialità medicinali particolari (es radiofarmaci, prodotti medicinali derivati dal sangue umano, erbe medicinali etc.)

CTD
COMMON TECHNICAL DOCUMENT

- E'applicabile a tutti i tipi di procedura e specialità medicinali.

- Obbligatorio dal 07/2003 e ora anche in eCTD

- E' costituito di 5 Moduli:

Modulo 1: informazioni amministrative, non armonizzato nelle tre Regioni (EU,US, J)

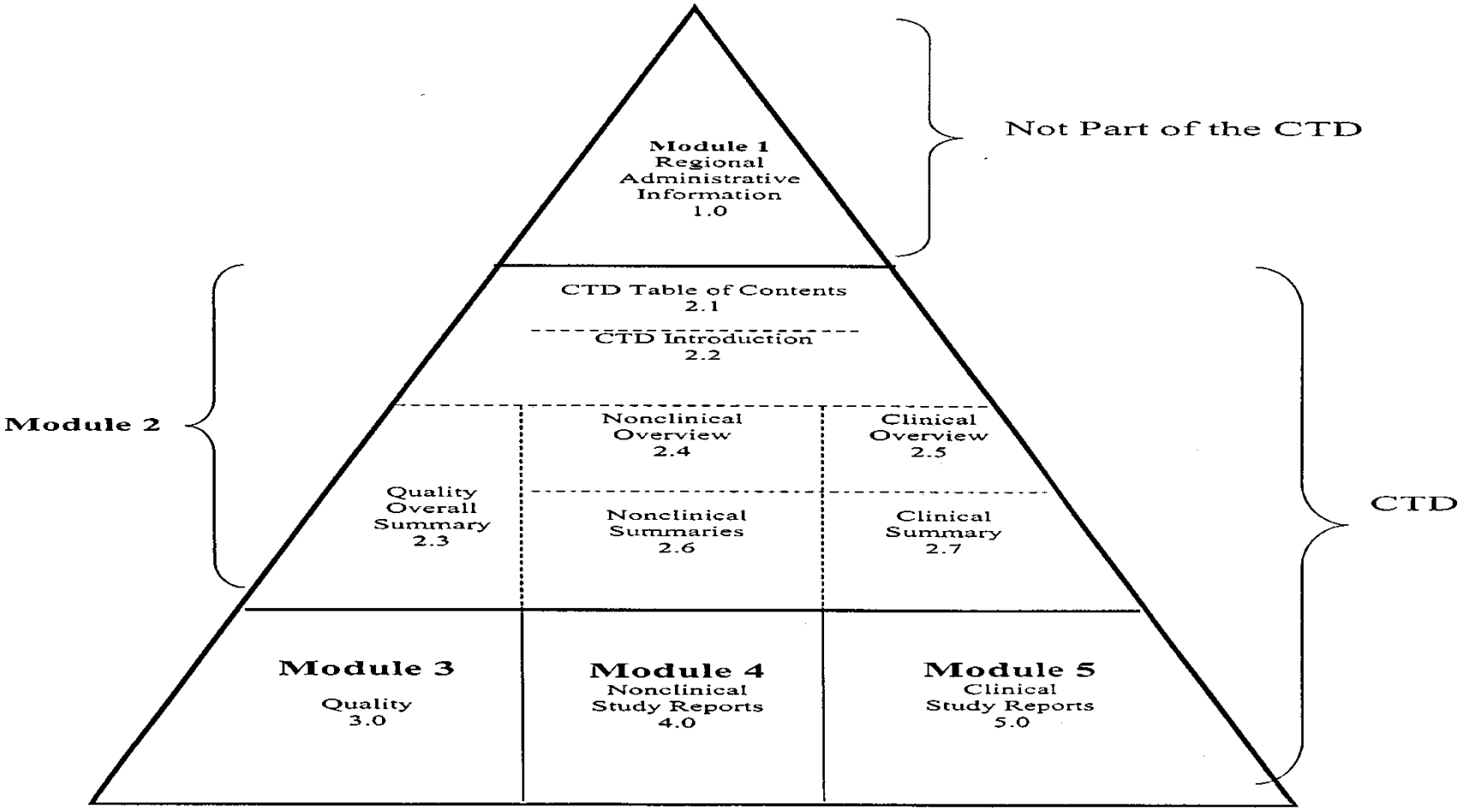
Modulo 2: Sommari

Modulo 4: documentazione farmacologica e tossicologica

Modulo 5: Documentazione clinica

CTD

Diagrammatic Representation of the Organization of the CTD
Common Technical Document



Chiesi

Module 1

European Union (EU)

Administrative Information
and Prescribing Information

This module should contain documents specific to each region, for example application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module 1 Table of Content

1.0 Cover letter

1.1 Comprehensive Table of Contents

1.2 Application Form

1.3 Product Information

- 1.3.1 SPC, Labeling and Package Leaflet
- 1.3.2 Mock – up
- 1.3.3 Specimen
- 1.3.4 Consultation with Target Patient Groups
- 1.3.5 Product Information already approved in the Member States
- 1.3.6 Braille

1.4 Information about the Experts

- 1.4.1 Quality
- 1.4.2 Non – clinical
- 1.4.3 Clinical

Module 1 Table of Content

1.5 Specific Requirements for Different Types of Applications

1.5.1 Information for Bibliographical Applications

1.5.2 Information for Generic, “Hybrid” or Bio-similar Applications

1.5.3 (Extended) Data/Market Exclusivity

1.5.4 Exceptional Circumstances

1.5.5 Conditional Marketing Authorization

1.6 Environmental Risk Assessment

1.6.1 Non – GMO

1.6.2 GMO

1.7 Information relating to Orphan Market Exclusivity

1.7.1 Similarity

1.7.2 Market Exclusivity

Module 1 Table of Content

1.8 Information relating to Pharmacovigilance

1.8.1 Pharmacovigilance System

1.8.2 Risk-management System

1.9 Information relating to Clinical Trials

1.10 Information relating to Paediatrics

Responses to Questions

Additional Data

Module 1.2: Application Form

Module 1.2 is to be used for an application for a Marketing authorisation of a medicinal product for human submitted to

- (a) the European Medicines Agency under the centralised procedure or
- (b) a Member State under either a national, mutual recognition or decentralised procedure

The different application forms are available on the Website of the European Commission (EUDRALEX, the collection of rules and regulations governing Medicinal products in the European Union)

The relevant application form has to be included, depending on the type of application

Module 1.3: Product Information

Summary of product characteristics (SPC), Labelling and Package Leaflet are included in the Module 1.3.1.

The SPC (about 5-15 pages) sets out the agreed position of the medicinal product as distilled during the course of the assessment process. As such the content Cannot be changed except with the approval of the originating competent Authority.

The SPC is the basis of information for health professionals on how to use the medicinal product safely and effectively. The Package Leaflet (PL) shall be drawn up in accordance with the SPC.

Module 1.3: Product Information

Patient information leaflets (PIL, Module 1.3.1) are leaflets containing information about Medical conditions, available services, and treatments.

It is a document provided along with a prescription medication to provide Additional information about that drug to patients.

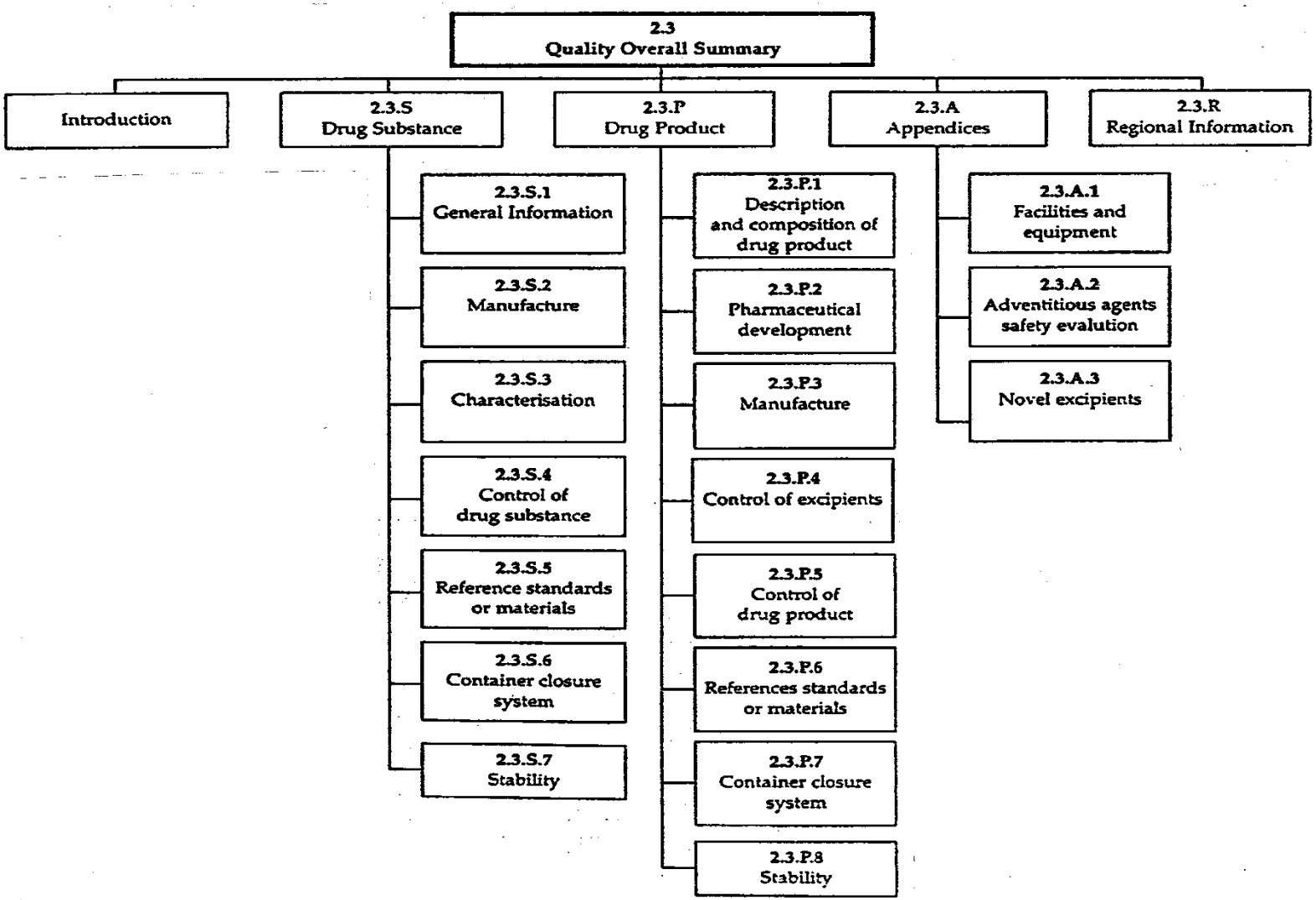
The “Guideline on packaging information” is the reference guideline to write the PIL (see Notice to Applicant Volume 2 C in EUDRALEX)

Module 1.8.1 Pharmacovigilance System

A detailed description of the pharmacovigilance system which the applicant will Introduce must be provided.

This should proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country according to Article (8) of Directive 2001/83/EC.

CTD MAP



Chiesi

MODULO 2

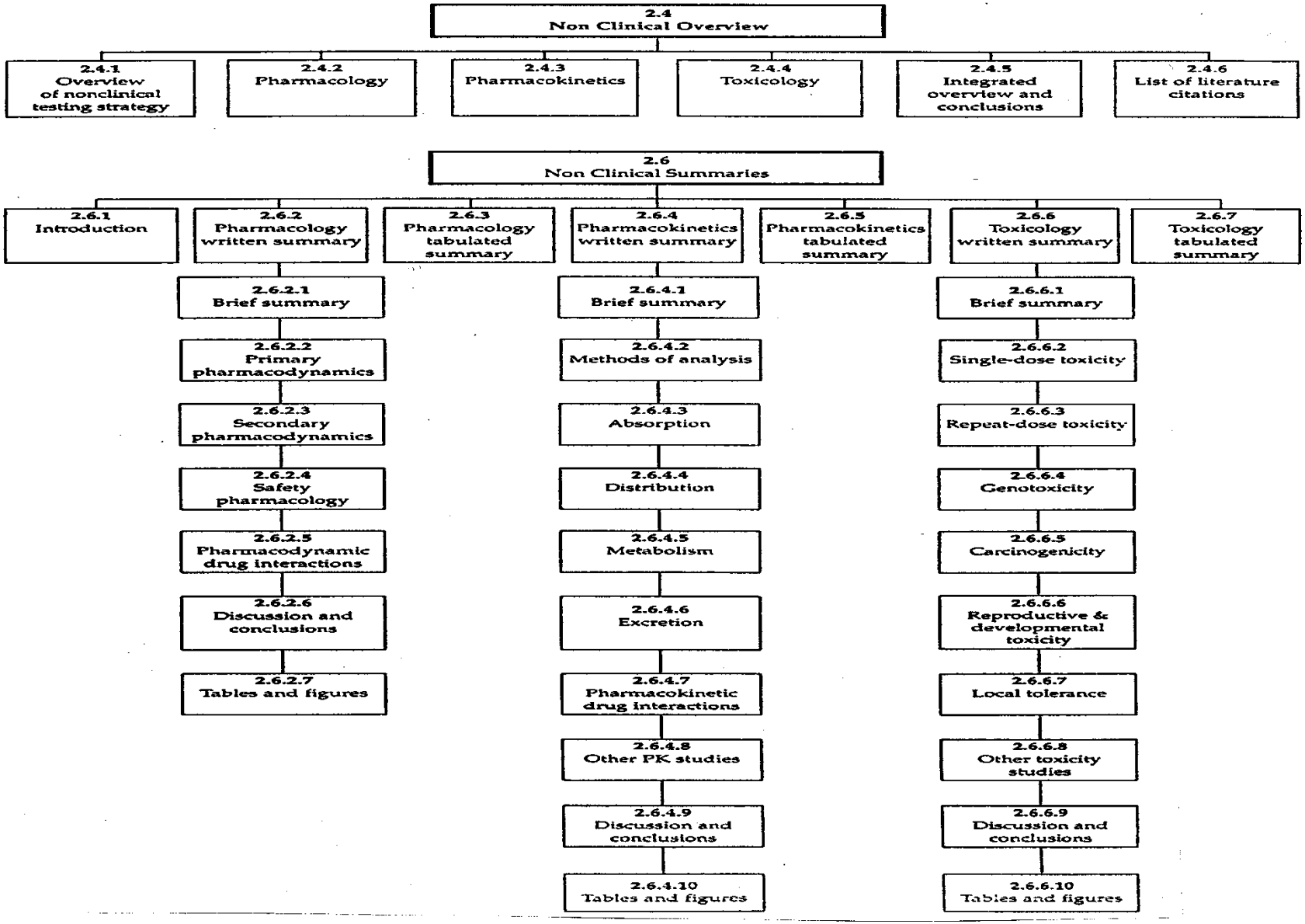
2.3 QUALITY OVERALL SUMMARY

- IL Quality Overall Summary (QOS) è un riassunto/riepilogo delle informazioni incluse nel Modulo 3. Ha la stessa granularità con un grado minore di dettaglio.

- Il QOS deve includere una discussione sugli argomenti principali sulla base dei dati riportati nel Modulo 3 e deve valutare i dati riportati anche negli altri Moduli che hanno impatto sulla qualità.

S DRUG SUBSTANCE
P DRUG PRODUCT
A APPENDICES
R REGIONAL INFORMATION

CTD


2.4
Non Clinical Overview
2.4.1
Overview of nonclinical testing strategy
2.4.2
Pharmacology
2.4.3
Pharmacokinetics
2.4.4
Toxicology
2.4.5
Integrated overview and conclusions
2.4.6
List of literature citations
2.6
Non Clinical 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
2.6.2.1
Brief summary
2.6.2.2
Primary pharmacodynamics
2.6.2.3
Secondary pharmacodynamics
2.6.2.4
Safety pharmacology
2.6.2.5
Pharmacodynamic drug interactions
2.6.2.6
Discussion and conclusions
2.6.2.7
Tables and figures
2.6.4.1
Brief summary
2.6.4.2
Methods of analysis
2.6.4.3
Absorption
2.6.4.4
Distribution
2.6.4.5
Metabolism
2.6.4.6
Excretion
2.6.4.7
Pharmacokinetic drug interactions
2.6.4.8
Other PK studies
2.6.4.9
Discussion and conclusions
2.6.4.10
Tables and figures
2.6.6.1
Brief summary
2.6.6.2
Single-dose toxicity
2.6.6.3
Repeat-dose toxicity
2.6.6.4
Genotoxicity
2.6.6.5
Carcinogenicity
2.6.6.6
Reproductive & developmental toxicity
2.6.6.7
Local tolerance
2.6.6.8
Other toxicity studies
2.6.6.9
Discussion and conclusions
2.6.6.10
Tables and figures

Chiesi

MODULE 2

2.4 NON CLINICAL OVERVIEW

- Valutazione integrata e critica degli aspetti farmacologici, farmacocinetici e tossicologici
- Discussione delle implicazioni non cliniche dei risultati degli studi nell'ottica della sicurezza sull'uomo (dai dati al product information)
- Valutazione finale sulla sicurezza della specialità medicinale adeguatamente commentata
- Commenti da riportare nel RCP (sezioni 4.6 e 5.3)

MODULE 2

2.6 NON CLINICAL WRITTEN AND TABULATED SUMMARIES

Preparation of format acceptable for non clinical pharmacology, pharmacokinetics and toxicology data

General presentation ordered by:

- species
- route
- duration

Sequence to follow (written tabulate)

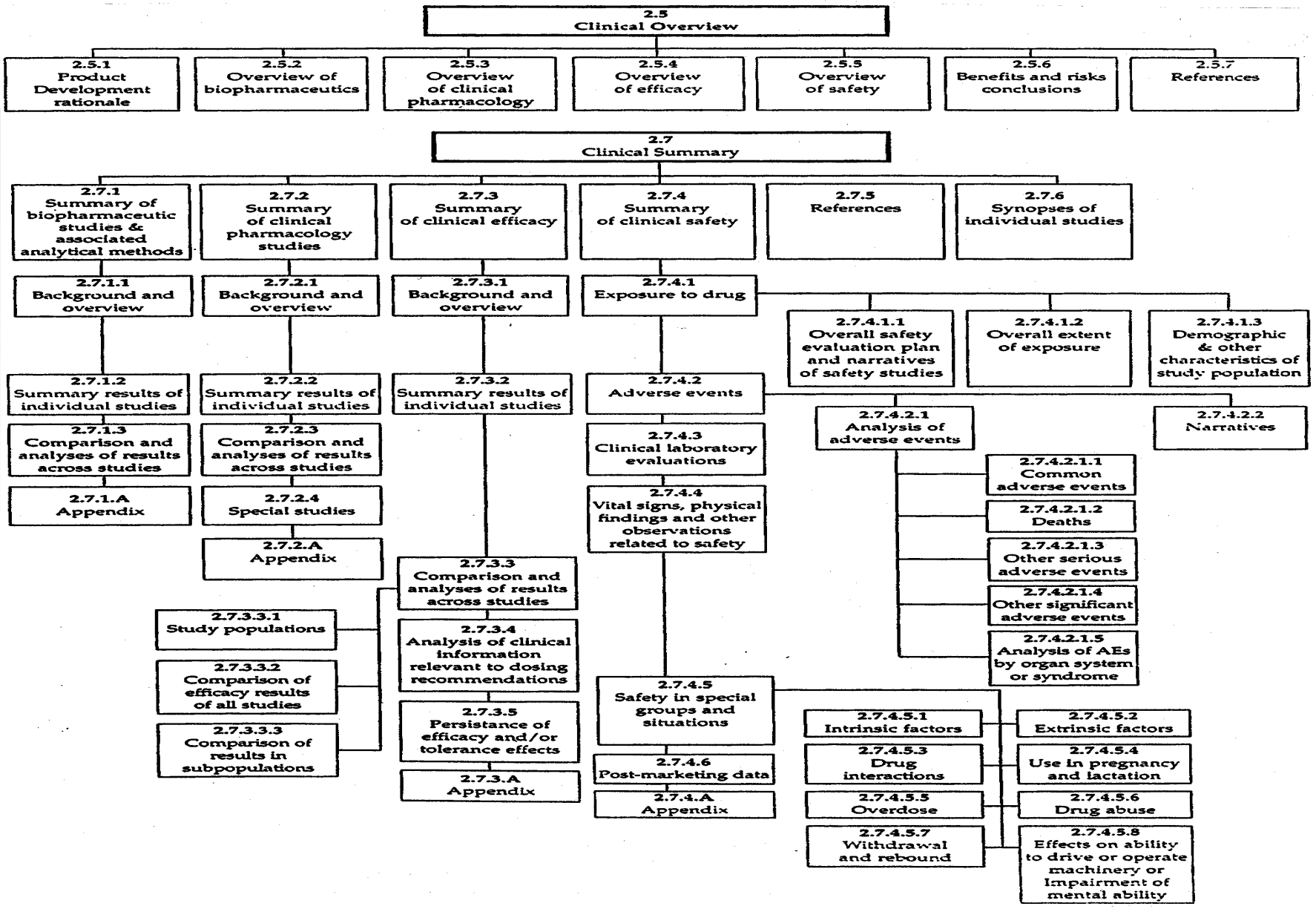
- pharmacology
- pharmacokinetics
- toxicology

MODULE 2

2.6 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

Devono essere descritti e tabulati gli studi non-clinici (farmacologia, farmacocinetica e tossicologia)

CTD


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 References
2.7 Clinical Summary
2.7.1 Summary of biopharmaceutic studies & associated analytical methods
2.7.2 Summary of clinical pharmacology studies
2.7.3 Summary of clinical efficacy
2.7.4 Summary of clinical safety
2.7.5 References
2.7.6 Synopses of individual studies
2.7.1.1 Background and overview
2.7.1.2 Summary results of individual studies
2.7.1.3 Comparison and analyses of results across studies
2.7.1.A Appendix
2.7.2.1 Background and overview
2.7.2.2 Summary results of individual studies
2.7.2.3 Comparison and analyses of results across studies
2.7.2.4 Special studies
2.7.2.A Appendix
2.7.3.1 Background and overview
2.7.3.2 Summary results of individual studies
2.7.3.3 Comparison and analyses of results across studies
2.7.3.3.1 Study populations
2.7.3.3.2 Comparison of efficacy results of all studies
2.7.3.3.3 Comparison of results in subpopulations
2.7.3.4 Analysis of clinical information relevant to dosing recommendations
2.7.3.5 Persistance of efficacy and/or tolerance effects
2.7.3.A Appendix
2.7.4.1 Exposure to drug
2.7.4.1.1 Overall safety evaluation plan and narratives of safety studies
2.7.4.1.2 Overall extent of exposure
2.7.4.1.3 Demographic & other characteristics of study population
2.7.4.2 Adverse events
2.7.4.2.1 Analysis of adverse events
2.7.4.2.1.1 Common adverse events
2.7.4.2.1.2 Deaths
2.7.4.2.1.3 Other serious adverse events
2.7.4.2.1.4 Other significant adverse events
2.7.4.2.1.5 Analysis of AEs by organ system or syndrome
2.7.4.2.2 Narratives
2.7.4.3 Clinical laboratory evaluations
2.7.4.4 Vital signs, physical findings and other observations related to safety
2.7.4.5 Safety in special groups and situations
2.7.4.5.1 Intrinsic factors
2.7.4.5.2 Extrinsic factors
2.7.4.5.3 Drug interactions
2.7.4.5.4 Use in pregnancy and lactation
2.7.4.5.5 Overdose
2.7.4.5.6 Drug abuse
2.7.4.5.7 Withdrawal and rebound
2.7.4.5.8 Effects on ability to drive or operate machinery or Impairment of mental ability
2.7.4.6 Post-marketing data
2.7.4.A Appendix

Module 2.5: Clinical Overview

- Analisi critica dei dati clinici contenuti nel Modulo 5
- Non deve solo ricapitolare i dati clinici, ma deve discuterli ed interpretarli
- Deve presentare i punti di forza e I limiti
- Analizzare i rischi e i benefici della specialità medicinale
- Discutere l'RCP proposto

MODULE 3: QUALITY

3.1 Table of Contents
3. 2 Body Data
3.3 Literature References

3.2.S DRUG SUBSTANCE
3.2.P DRUG PRODUCT
3.2.A APPENDICES
3.2.R REGIONAL INFORMATION

The “Body of Data” in this guideline merely indicates where the information should be located.

MODULE 3.2.S

3.2.S.1 General Information
3.2.S.2 Manufacture
3.2.S.3 Characterization
3.2.S.4 Control of Drug Substance
3.2.S.5 Reference Standards or Materials
3.2.S.6 Container Closure System
3.2.S.7 Stability

MODULE 3.2.S

3.2.S.1 General Information

Information on the nomenclature of the drug substance should be provided.

For example:

- Recommended International Non-proprietary Name (INN);
- Compendial name (e.g. European Pharmacopoeia) if relevant;
- Chemical name(s);
- Company or laboratory code;
- Other non-proprietary name(s), e.g., national name

Es. Bicalutamide

(±)-N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulphonyl]-2-hydroxy-2-methylpropanamide

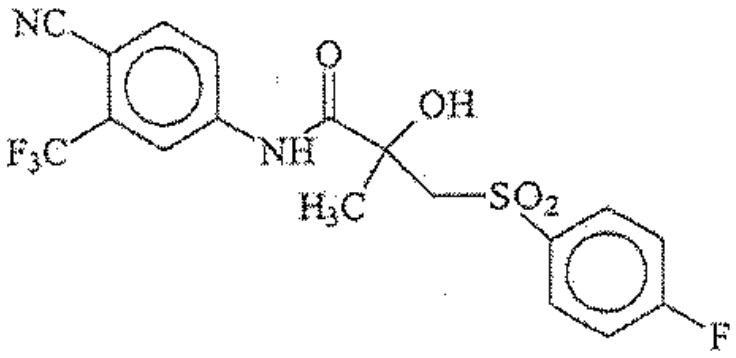
MODULE 3.2.S

3.2.S.1 General Information

Structure:

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided

E.g.:



MODULE 3.2.S

3.2.S.1 General Information

General properties

A list of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech should be provided.

E.g. Solubility, Physical Characteristics (es. Appearance, pKa, Melting range, Stereochemistry characteristics: R/S percentage of isomers), pH, Polymorphism, Biological activity etc.)

MODULE 3.2.S

3.2.S.2 Manufacture

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls.

Process Controls include in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in **Controls of Critical Steps and Intermediates**).

Process Controls are checks performed during production in order to monitor and, if Appropriate, to adjust the process and/to ensure that the intermediate or API conforms to its Specifications.

Ex: Temperature, pH, tests on materials, process tests etc.

MODULE 3.2.S

3.2.S.2 Manufacture

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps, previously identified, should be provided in the section **Controls of Critical Steps and Intermediates**.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process.

MODULE 3.2.S

3.2.S.3 Characterisation

- Confirmation of structure based on e.g., synthetic route and spectral analyses
- Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs.

E.g. Bicalutamide

The general data (Structural formula, Relative molecular mass)

Analytical results prove the structural formula (NMR analysis, CNMR analysis, Mass Spectrum). You should report tabular forms of results and raw data (spectrums).

Data about polymorphism eg. XR Power Diffraction.

MODULE 3.2.S

3.2.S.3 Characterisation

Polymorphism is the ability of a solid material to exist in more than one form or crystal structure and it has impact on different parts of the CTD:

– 3.2.S 1.3 List of all properties: Polymorph of interest
– 3.2.S 3.1 Studies on Polymorphism (experimental data)
– 3.2.P 2 Influence of the polymorphic forms on the formulation
– 3.2.S 4.1 Specifications of the active ingredient
– 3.2.S.4.2 Analytical procedures
– 3.2.S.4.2 Validation of the analytical procedures
– 3.2.S.4.4 Batch analysis
– 3.2.S 4.5 Justification of Specifications
– 3.2.P 5.1 Specifications of the finished product
– 3.2.P 5.6 Justification of Specifications

Many analytical procedures could be used: XR Power Diffraction, Solide-state IR or NMR, DSC/TGA, RAMAN spectroscopy in order to describe different conditions responsible for the development of polymorphs.

MODULE 3.2.S

3.2.S.3 Characterisation

Impurities may be classified into the following categories:

· Organic Impurities (Process and Drug Related, eg starting materials, intermediates, degradation products etc.)

· Inorganic Impurities (catalyst, reagents, Heavy metals etc)

· Residual Solvents

What information about impurities?

- Structural formula
- Chemical and physical data
- Analytical procedures used to identify them
- Summary of the studies

Limits of impurities should be justified from safety studies if necessary.

MODULE 3.2.S

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification (name, manufacturer)

3.2.S.4.2 Analytical Procedures (name, manufacturer)

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

3.2.S.4.4 Batch Analyses (name, manufacturer)

3.2.S.4.5 Justification of Specification (name, manufacturer)

MODULE 3.2.S

3.2.S.4 Control of Drug Substance

Specifications: tests, procedures, and acceptance criteria
which play a major role in assuring the quality of the new drug substance and new drug product at release and during shelf life.
If the monography of the active substance is present in the Phe Eur. the Applicant should apply specifications reported in the monography.

E.g.: Bicalutamide
Description, Identification (IR), Identification (XRD), Water content, Sulphated Ash, Heavy metal, Assay (HPLC), Optical Rotation, Residual solvents (GC), Impurities (HPLC).

MODULE 3.2.S

3.2.S.6 Control of Drug Substance

Analytical procedures used to release batches of the active substance should be described or in alternative should be reported the reference to European Pharmacopeia.

Information about the validation of the analytical procedures should be reported, in particular experimental data of the validations.

Data on the Accuracy, Precision, Reproducibility, Specificity and Linearity of Analytical methods should be reported.

Data on LOQ (limit of the quantification) and LOD (Limit of the Identification) should be reported

3.2.S. Drug Substance

3.2.S.6 Container Closure System

A description of the container closure system(s)

Identity of materials of construction of each primary packaging component, and their specifications.

The specifications should include description and identification of materials

Non-compendial methods (with validation) should be included, where appropriate

3.2.P. Drug Product

3.2.P Drug Product

3.2.P.1 Description and Composition

3.2.P.2 Pharmaceutical Development

3.2.P.3 Manufacture

3.2.P.4 Control of Excipients

3.2.P.5 Control of Drug Product

3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System

3.2.P.8 Stability

3.2.P. Drug Product

3.2.P Description and Composition

A description of the drug product and its composition for example:

• the dosage form

• Composition, i.e., list of all components of the dosage form, and the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications):

• Description of accompanying reconstitution diluent(s)

• Type of container and closure used for the dosage form

E.g. Film-coated tablets

Table 3.2.P.1/1: Composition of XXX Y mg film-coated tablets **tablets**

Ingredients	**Unit formula per tablet (mg)**	**Function**	**Standard**
Active ingredient	XX	active	3.2.S.5
Excipient 1	XX	diluent	Ph. Eur.
Excipient 2	XX	disintegrant	USP/NF
Excipient 3	XX	binding agent	Ph. Eur.
Excipient 4	XX	film	Internal monograph

3.2.P. Drug Product

3.2.P.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application.

3.2.P.2.1 Components of the Drug Product (name, dosage form)

3.2.P.2.2 Drug Product (name, dosage form)

3.2.P.2.3 Manufacturing Process Development

3.2.P.2.4 Container Closure System

3.2.P.2.5 Microbiological Attributes

3.2.P.2.6 Compatibility

3.2.P. Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product (Film-Coated tablets).

Studies to demonstrate the compatibility between the drug substance and the excipients (ex. DSC and chromatographic techniques)

Discussion and data on the chemo-physical characteristics of the Drug substance conditioning the characteristics of the Drug product (solubility, polymorphism, particle size, hygroscopic profile).

Justification about the selection of the excipients

3.2.P. Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.2.2 Drug product (Film-Coated tablets).

Short description of the development of the medicinal products (results on the dissolution studies or bioequivalence)

Enquiring about most important chemo-physical and biological parameters conditioning the performances of the drug product (eg dissolution studies and polymorphisms studies)

3.2.P. Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.2.2 Container Closure System (Film-Coated tablets).

- Description selection criteria of primary closure system
- Choice of the material
- Protection from light
- Protection from humidity
- Compatibility with the Drug product

The Justification of the compatibility with the use of dosage devices should be reported in the section 3.2.P.2.6.

3.2.P. Drug Product

3.2.P.5 Control of Drug Product

- Specifications of the drug product
- The analytical procedures used for testing the drug product
- Analytical validation information, including experimental data, for the analytical Procedures used for testing the drug product
- A description of batches and results of batch analyses
- Information on the characterisation of impurities, if not previously provided in drug substance.
- Justification for the proposed drug product specification(s)

3.2.P. Drug Product

3.2.P.5 Control of Drug Product

E.g. Analytical procedures. Tablets

1 Physical, Technological and Microbiological Controls

1.1 Appearance

Visual inspection.

1.2 Mean Weight and Weight Uniformity

Perform the test in accordance to Ph. Eur. current edition

1.3 Equilibrium Relative Humidity (ERH)

Perform the control using a XX apparatus for equilibrium relative humidity determination. The instrumental characteristics and its working principle are reported in Attachment 3.2.P.5.2_1.

1.4 Microbial Count

Perform the test on a periodic basis (1 out of 10 batches) according to Ph. Eur. current edition (2.6.12 - 2.6.13 - 5.1.4).

1.5 Packaging

The final packaging has to comply with the standard sample, exactly defined in the product specifications, for quality and quantity of the content and for correctness of the wordings. The batch code and the expiry date must be exact and clearly legible.

3.2.P. Drug Product

3.2.P.5 Control of Drug Product

2 Chemical Controls

2.1 HPLC Identity of the Active ingredient

Under the analytical conditions described in the following paragraph for the quantitative assay, the active ingredient is identified for the presence of one peak, in the chromatogram of the test solution, having the same retention times as those present in the reference standard solution.

2.2 Active ingredient content

The assay is performed by HPLC.

Equipment and operating conditions

HPLC Waters system or similar with UV variable wavelength detector

- Column Specifications.
- Flow: 1.2 ml/min.
- Mobile phase: A) XX
  B) XX

Elution in gradient according to the reported scheme.

…..

2.3 Impurities/degradation products assay

2.3.1 Active ingredient impurity/degradation product (DKP) assay

STABILITY

3.2.S.7 and 3.2.P.8 Stability

The purpose of stability testing is to provide on how the quality of a drug substance or drug product varies with the time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life of the drug product and recommended storage conditions

Shelf life: the time interval that a drug product is expected to remain within the approved shelf life specification provided that it is stored under the conditions defined on the label in the proposed containers and closure.

Retest period: the period of time during which the drug substance can be considered to remain within the specification and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under the defined conditions after this period, the batch should be retested for compliance with specification and then used immediately.

STABILITY

3.2.S.7 and 3.2.P.8 Stability

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf life.

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative

Information on the analytical procedures used to generate the data and validation of these procedures should be included if not described in the sections 3.2.S.4 or 3.2.P.5.

STABILITY

3.2.S.7 and 3.2.P.8 Stability

3.2.P.8.1/1 Shelf-life Specifications of XX Tablets

Test	Method	Specification
Appearance of product	Visual inspection	White tablets with upper scoring line
Average weight* (mg)	Ph. Eur.	XX-YY
Weight uniformity	Ph. Eur.	, XX ± 15% of mean weight
Equilibrium relative humidity (ERH) (%)	Novasina	≤ 11
Identification*: Active ingredient	HPLC	Positive
Content (mg/tablet): Active ingredient	HPLC	XX-YY
		2.250-2.625
Content uniformity Indapamide* (mg/tablet)	HPLC	Complies with Ph. Eur.
Impurities/degradation products assay: DKP (% referring to active ingredient)	HPLC	≤ 5.0
AMI (%Referring to Indapamide)		≤ 1
Dissolution ** (% dissolved in 30 min): Active ingidient	Ph. Eur. HPLC	≥ 80
		≥ 50
Microbial count: Aerobic bacteria	Ph. Eur.	Category 3 A: ≤ 10^3 CFU/g
Fungi		≤ 10^2 CFU /g
E. coli		absent in 1 g
Packaging	Visual inspection	Complies with internal specs

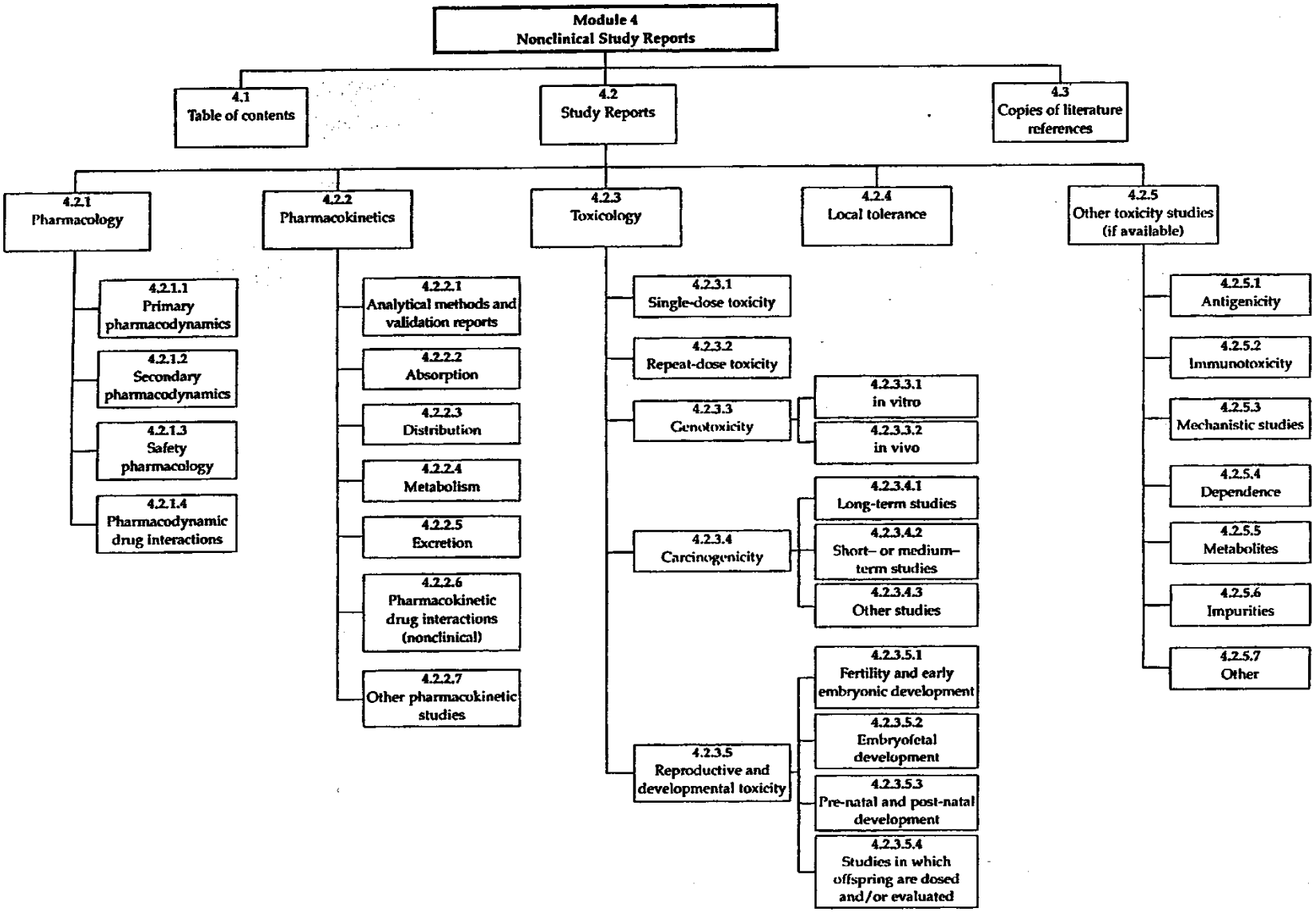
STABILITY

3.2.S.7 and 3.2.P.8 Stability

Medicinal product: XXX
Active ingredients: XXX
Dosage strength: XX mg/tablet
Batch No.: XXXX manufactured in XXX
Primary packaging: XXXX
Storage conditions: 21-24°C and 52-60 % R.H.

Time (months)	Appearance	ERH (%)	Disintegr. time*** (min)	XXXX				XXXXX			
				mg/tab.	Residue (%)	DKP (%)	Dissolution (% in 30 min)	mg/tab	residue (%)	AMI (%)	Dissolution (% in 30 min)
start	White tablets	36.2*	7	30.30	100.0	0.8	99.0	2.54	100.0	n.d.	64.0
9	Unchanged	8.0	6	30.24	99.8	1.1	97.5	2.54	100.0	<1**	61.5
12	Unchanged	8.4	6	30.84	101.8	1.3	97.8	2.51	98.8	n.d.	64.7
18	Unchanged	9.1	8	30.69	101.3	1.3	98.6	2.56	100.8	n.d.	64.8
24	Unchanged	8.8	6	30.33	100.1	1.6	97.6	2.55	100.4	<1**	64.2
36	Unchanged	10.3	6	30.75	101.5	1.8	100.7	2.57	101.2	<1**	62.8

CTD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Module 4

Non Clinical Study Reports

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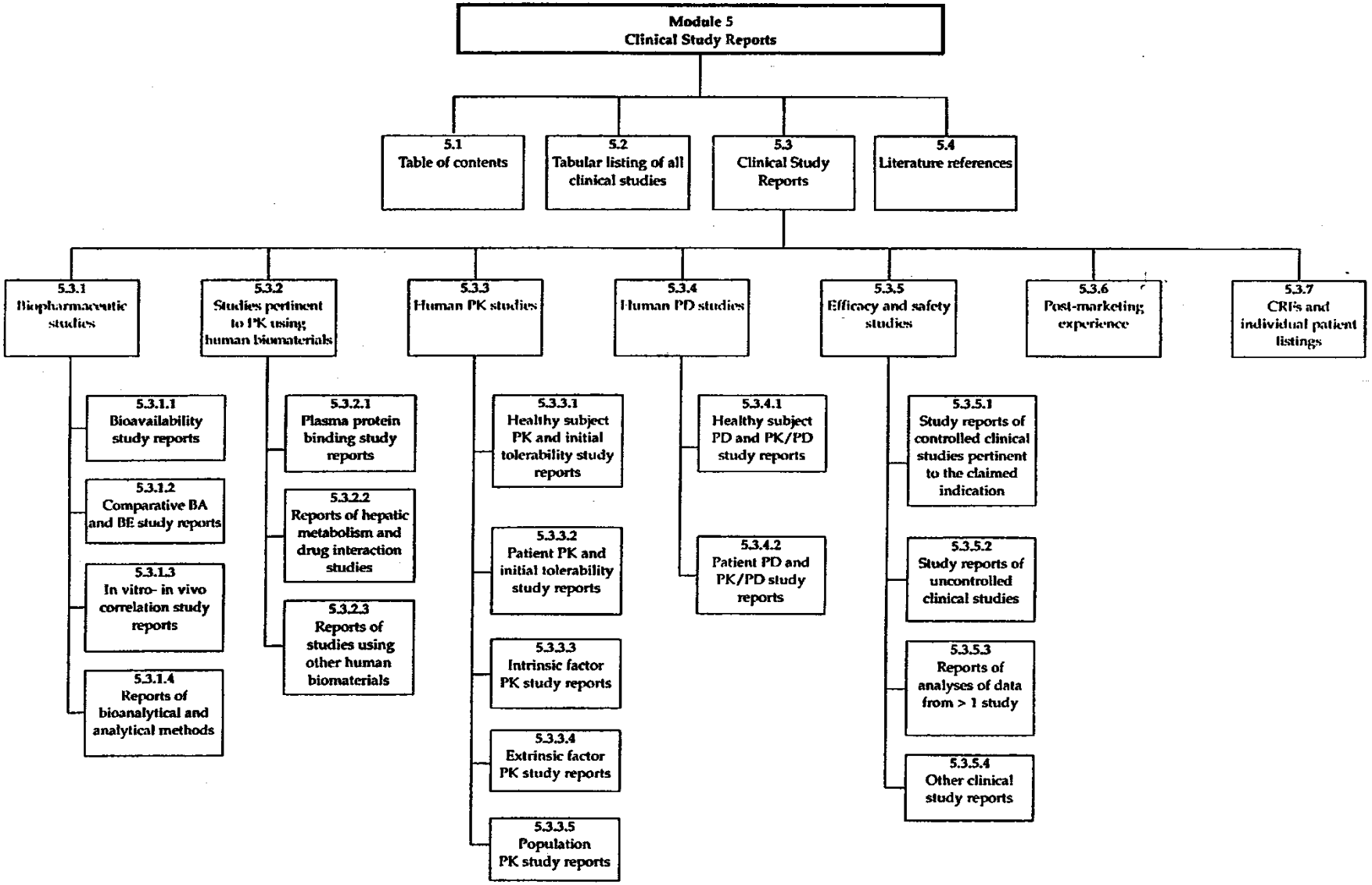
CTD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Module 5

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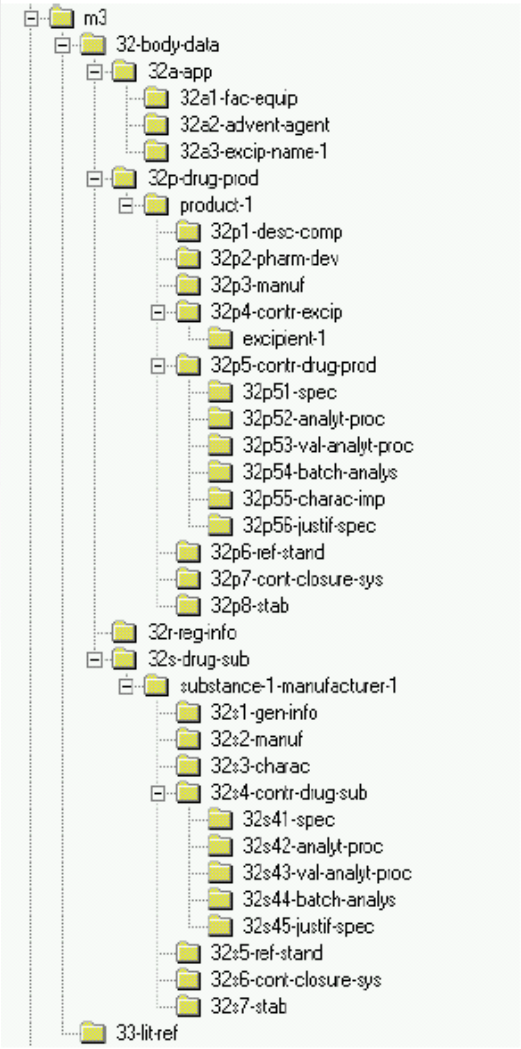
eCTD

The eCTD is defined as an interface for industry–to-agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission.

eCTD Structure



The overall architecture of the eCTD is designed to provide a commonly agreed upon submission and submission structure that imposes minimal restriction to the industry and agencies.

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Q&A

CONTACT:

A.SarziSartori@chiesi.com