GUIDANCE FOR INDUSTRY

ON PREPARATION OF

COMMON TECHNICAL DOCUMENT FOR IMPORT / MANUFACTURE AND MARKETING APPROVAL OF NEW DRUGS FOR HUMAN USE

(NEW DRUG APPLICATION – NDA)

DRAFT GUIDANCE

This guidance documents is for feedback purpose only
Comments and suggestion on this document should be submitted within 60 days of publication to
CDSCO, FDA Bhavan
Kotla Road, New Delhi – 110002

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
DIRECTORATE GENERAL OF HEALTH SERVICES
MINISTRY OF HEALTH & FAMILY WELFARE
GOVT. OF INDIA, NOVEMBER 2010

1 ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BA	Bioavailability
BE	Bioequivalence
CD	Compact Disc
CDSCO	Central Drugs Standard Control Organization
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
FSC	Free Sale Certificate
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
INR	Indian National Rupee
iv	intravenous
MA	Market Authorization
NDA	New Drug Application
NRA	National Regulatory Authority
OCR	Optical Character Recognition
PD	Pharmacodynamics
PK	Pharmacokinetics
po	*per oral*
QOS	Quality Overall Summary
WHO	World Health Organization

2 TABLE OF CONTENTS

GUIDANCE FOR INDUSTRY

ON PREPARATION OF COMMON TECHNICAL DOCUMENT FOR IMPORT / MANUFACTURE AND MARKETING APPROVAL OF DRUGS FOR HUMAN USE

(NEW DRUG APPLICATION - NDA)

3 BACKGROUND

Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by Central Drugs Standard Control Organization (CDSCO). The regulations under Drugs and Cosmetics Rules 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing.

Substantial documentation and data are required in these types of submissions, resulting in large, complex applications. Till date, applicants have used many different approaches in organizing the information and the differences in organization of data in each application has made reviewing more difficult and can also lead to omission of critical data or analyses. Such omissions can result in unnecessary delays in approvals. Thus, a common format of submission will help in overcoming these hurdles. Through the International Conference on Harmonisation (ICH) process, the Common Technical Document (CTD) guidance's have been developed for Japan, European Union, and United States.

Most countries have adopted the CTD format. Hence, CDSCO has also decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use. The same is already in use for biological products since 2009 and now this guidance document describes the format for preparation of CTD for marketing approval of pharmaceuticals for human use other than biological products (vaccines, biotechnology products, stem cell products, etc).

It is apparent that this structured application with comprehensive and rational contents will help the CDSCO to review and take necessary actions in a better way and would also ease the preparation of electronic submissions, which may happen in the near future at CDSCO.

This guidance is developed by CDSCO based on

- The ICH Harmonised Tripartite Guideline on "Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use". M4, *Step 4* version dated January 13, 2004, and
- Drugs & Cosmetics Act 1940 and Rules made thereunder.

4 SCOPE

- This guideline applies to import / manufacture and marketing approval of new drugs including New chemical entity, new indication, new dosage forms, modified release form, new route of administration etc. under the definition of new drug under Rule 122E of Drugs & Cosmetics rules as a finished pharmaceutical product.
- This guideline is not intended to advice on the design of studies that are required for product registration, but, indicates an appropriate format for submission of the data that have been acquired. Drugs & Cosmetics Act and Rules there under, defines the 'content requirements' for the specific type of submission and hence, this guidance document has to be read along with Drugs and Cosmetics Act 1940 and Rules made thereunder.

5 GENERAL CONSIDERATIONS

- The CTD is only a format for submission of information to CDSCO. It does not define the content.

- Although adherence to overall CTD structure is necessary, it should be noted that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format at some of the subsection levels, if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation.

- Clear and unequivocal information should be provided.

- Text and tables should be prepared using margins that allow the document to be printed clearly without losing any information and the left-hand margin should be sufficiently large so that information is not obscured by the method of binding.

- You can submit documents printed on both sides of a page, however, one should take care that the information is not obscured when the page is placed in a binder.

- Font sizes for text and tables should be of a style and size that are large enough to be easily readable. Times New Roman, 12-point font is recommended for descriptive text and Times New Roman, 9 to 10-point font for table contents and text.
- Document Pagination and segregation:
  - Entire submission should never be numbered consecutively by page. Page numbering should be at the document level and not at the volume or module level.
  - Every document should be numbered starting at page one, except for individual literature references, where the existing journal page numbering is considered sufficient.
  - All pages of a document should include a unique header or footer that briefly identifies its subject matter. Alternatively, a similar identifier should be used on a tab that precedes the document, to facilitate finding that document within the dossier.
  - If a section contains more than one document, a specific table of contents for that section can be included in the tab to identify the chronology and titles of the documents contained therein.
- All abbreviations should be defined at the first instance they are used and listed at the end of the dossier.
- References should be cited in accordance with the current edition of the *uniform requirements for manuscripts submitted to biomedical journals*, International Committee of Medical Journal Editors (ICMJE).

- Submission requirements / methodology
  - Please submit ONE hard copy and THREE soft copies i.e. Compact Disc (CD) (PDF format) of the dossier.
  - Hard copy: Sides and front of each volume/ file /binder must be labeled with the name of the applicant company, date of submission, name of the drug(s) and the file number (Numbering of files: 'x' of 'y' files e.g. if there are 10 files, file number 6 will be labeled as File No. 6 / 10).
  - Use of multiple volumes/ files/ binders is recommended than binding all the documents and modules in a very huge file. Preferably volumes/ files /binders should not be more than 3 inches thick and use of good quality binders is recommended. All the files should be kept together, bound by a good quality wire or thread (If there are too many volumes e.g. more than 10, then multiple grouping should be done).
  - CDs have to be labeled using a marker pen with the name of the applicant company, date of submission and name of the drug(s). If there are multiple CDs for one submission dossier, then the numbering as mentioned above should be followed. Scanned copies of only signed documents like test reports, signature pages will be acceptable and rest of the document has to be in PDF format with optical character recognition (OCR). The table of content under each head should be linked to the files (s) or relevant document for easy tracking in CD's.
  - Applicant should preserve a duplicate copy of the submitted dossier for any future reference and should be able to submit multiple copies, if required by CDSCO.

- All sentences in blue *italic* fonts are instructions to the applicant and the same when present in the templates has to be deleted before finalizing the documents.
- During cross-referencing from one module to other modules, please mention the volume, CTD module, tab identifier and page number of the other referring document/ section.

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
CDSCO CDSCO
MINISTRY OF HEALTH, GOVERNMENT OF INDIA

5.1 FURTHER CLARIFICATIONS

1. SOURCE OF BULK DRUG(S) FOR MANUFACTURING FINISHED FORMULATION

Documentations required related to source of bulk drug(s) /raw material(s) when the applicant is seeking approval for manufacturing of finished formulation only.

If the applicant has a manufacturing permission for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

CLARIFICATION: In case if the applicant does not have an approval from DCGI to manufacture the Active Pharmaceutical Ingredient(s) (API), then the applicant can,

- Import the API → Applicant has to submit all relevant information and documents listed in this CTD and comply with further requirements for import of API.
- Manufacture the API → Applicant has to submit all relevant information and documents listed in this CTD and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approved by DCGI → In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury challan of requisite amount with all relevant documents. Approval of manufacture of new

drug finished formulation will be considered after approval of manufacture of the API.

2. IS CTD MANDATORY FOR ALL TYPE OF SUBMISSIONS?

CTD is mandatory for all

- Import and/or manufacture and marketing approval of new drugs (New chemical entity, new indication, new dosage forms, new route of administration etc.), as a finished pharmaceutical product, for first time submission and for subsequent applications until 4 years.
- Modified release formulations (even after 4 years of approval by CDSCO)
- Fixed Dose Combinations under item (a) of Appendix VI of Schedule Y of Drugs and Cosmetics Rules 1945.

However, the details and depth of documentation will vary with the type of applications.

NOTE: This CTD guidance document is not applicable for the manufacture and sale of bulk drugs of a new drug approved in the country. In case of a new chemical entity, the approval of only API cannot be considered unless safety and efficacy of the finished formulation of the drug is evaluated and approved by this office.

6 GUIDELINES FOR PREPARATION OF CTD

6.1 CTD: OVERVIEW

The CTD is organized into five modules (Module 1, 2, 3, 4, and 5) and a diagrammatic representation of organization of the CTD is provided in **Annexure I**.

Module 1: General Information

This module should contain documents specific to India; for example, Form 44, Treasury challan fee or the proposed label for use in India. Details to be provided are further explained in *Section 6.2* of this document.

Module 2: CTD Summaries

This module should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use, not exceeding one page. Module 2 should contain 7 sections in the following order:

- CTD table of contents
- CTD introduction
- Quality overall summary
- Nonclinical overview
- Clinical overview
- Nonclinical written and tabulated summaries
- Clinical summary

The organization of these summaries is described further at *Section 6.3* of this document.

Module 3: Quality

Information on Quality should be presented in the structured format as described in *Section 6.4* of this document.

Module 4: Nonclinical Study Reports

The nonclinical study reports should be presented in the order described at *Section 6.5* of this document.

Module 5: Clinical Study Reports

The human study reports and related information should be presented in the order described at *Section 6.6* of this document.

The overall organization of the CTD is presented on the following pages.

CDSCO CDSCO

6.2 MODULE 1: GENERAL INFORMATION

MODULE 1: GENERAL INFORMATION	
1.1	**COVERING LETTER & COMPREHENSIVE TABLE OF CONTENTS (MODULES 1 TO 5)**
1.2	**ADMINISTRATIVE INFORMATION**
1.2.1	**Brief introduction about the applicant company**
1.2.2	**Duly filled and signed application in Form 44 and Treasury Challan** (copy of treasury challan when the fee is already paid during clinical trial application)
1.2.3	**Legal and Critical Documents**
1.2.3.1	*General, as applicable* a. Copy of Clinical Trial/BE No Objection letters issued by CDSCO b. Copies of any other relevant competent authority clearances/ approvals / no objection certificates obtained or any key communication letters with authorities.
1.2.3.2	*For import and marketing of finished products* a. Copy of drug sale license in Form 20B / 21B b. Copy of Free Sale Certificate (FSC) and/or Certificate of Pharmaceutical Products (CPP) issued by the Regulatory Authority of the country of origin / Free sale certificate issued by the Regulatory Authorities of

	other major countries. c. Batch release certificate issued by National Regulatory Authorities d. Copy of Form 11 for imported drug product for testing purpose
1.2.3.3	*For manufacture and marketing of finished products (This also includes import of raw materials and manufacture of finished formulations)* a. Copy of existing manufacturing license in Form 25 / 28 / 26 b. Copy of Form-29
1.2.3.4	*Undertaking or Declaration as per* ***Annexure II***
1.2.3.5	*Certificate of Analysis*
1.2.4	**Coordinates related to the application**
1.2.4.1	*Name, address, telephone, fax, e-mail of applicant of drug product*
1.2.4.2	*Name, address, telephone, fax, e-mail of manufacturer of drug substance*
1.2.4.3	*Name, address, telephone, fax, e-mail of the responsible official*
1.2.4.4	*Name, address, telephone, fax, e-mail of other manufacturer(s) involved in the production process*
1.2.4.5	*Name, designation, address, telephone, fax, e-mail of the official responsible for releasing batches of drug product*

1.2.4.6	*Name, address, telephone, fax, e-mail of the authorized agent in India: (for imported drug products)*
1.2.4.7	*Name, address, telephone, fax, e-mail of the manufacturing premises holding Market Authorization of the drug product (for imported drug products)*
1.3	**GENERAL INFORMATION ON DRUG PRODUCT**
1.3.1	**A brief description of the drug and the therapeutic class to which it belongs**
1.3.2	**Non-proprietary name or generic name of drug**
1.3.3	**Composition** (As per label claim)
1.3.4	**Dosage form**
1.3.5	**Strength per dosage unit**
1.3.6	**Dispensing requirements**
1.3.7	**Route of administration**
1.3.8	**Commercial presentation**
1.3.9	**Conditions of storage or conservation**
1.3.10	**Full Prescribing Information (Package insert)** The prescribing information (package insert) shall comprise the following sections: Generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic

	properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.
1.3.11	**Product Labeling: Proposed draft labels and cartons have to be provided.** (The drafts of label and carton texts should comply with provisions of rules 96 and 97 of the Drugs and Cosmetics Rules 1945.) a. Primary package label b. Secondary package label
1.3.12	**Summary of the packaging procedures** for Indian shipments (including box sizes, packing volumes).
1.4	**SUMMARY OF TESTING PROTOCOL(S) FOR QUALITY CONTROL TESTING together with a complete impurity profile and release specifications for the product should be submitted.**
1.5	**REGULATORY STATUS IN OTHER COUNTRIES**
1.5.1	**List of countries where proposed drug is Marketed**
1.5.2	**List of countries where proposed drug is Approved for Marketing**
1.5.3	**List of countries where proposed drug is Approved as IND**
1.5.4	**List of countries where proposed drug is Withdrawn** (if any, with reasons for withdrawal)
1.5.5	**Details of any restrictions on use, in any country where it is marketed /approved**
1.6	**DOMESTIC PRICE OF THE DRUG FOLLOWED IN THE**

	COUNTRIES OF ORIGIN IN INR.
1.7	**A BRIEF PROFILE OF THE MANUFACTURER'S RESEARCH ACTIVITY**
1.8	**A BRIEF PROFILE OF THE MANUFACTURER'S BUSINESS ACTIVITY IN DOMESTIC AS WELL AS GLOBAL MARKET**
1.9	**INFORMATION REGARDING INVOLVEMENT OF EXPERTS, IF ANY**
1.10	**SAMPLES OF DRUG PRODUCT:** Samples of drug substance and drug product (an equivalent of 50 clinical doses or double the quantity required (whichever is more) for complete testing of product with testing protocols, full impurity profile and release specifications should be forwarded to Central Drugs Laboratory, as and when required / instructed.
1.11	**PROMOTIONAL MATERIALS**

6.3 MODULE 2: CTD SUMMARIES

MODULE 2: CTD SUMMARIES	
2.1	**TABLE OF CONTENTS OF MODULE 2**
2.2	**INTRODUCTION** This should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).
2.3	**QUALITY OVERALL SUMMARY**
Note: In general, the Quality Overall Summary (QOS) is an outline of data presented in Module 3. Please do not provide the entire information present in Module 3 corresponding sections, but, provide brief information picked from relevant sections. This QOS normally should not exceed 40 pages of text, excluding tables and figures. The underlined text below indicates where tables, figures, or other items can be imported directly from Module 3.	
2.3.S	**SUMMARY OF DRUG SUBSTANCE**
2.3.S.1	**General Information (name, manufacturer)** Brief information from 3.2.S.1 should be included. The source of bulk drug(s) /raw material(s) - If the applicant has a manufacturing permission for bulk drugs, please provide a copy of the same and further details under drug substance can be very brief. Otherwise, provide the consent letter from the approved

	source regarding supply of material.
2.3.S.2	**Manufacture (name, manufacturer)** Information from 3.2.S.2 should be included: Information on the manufacturer; A flow diagram, as provided in 3.2.S.2.2; A brief description of the, ▪ manufacturing process and the controls ▪ source and starting material and raw materials of biological origin used ▪ Selection and justification of critical manufacturing steps, process controls, and acceptance criteria. ▪ process validation and/or evaluation ▪ major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency
2.3.S.3	**Characterisation (name, manufacturer)** A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included. When a drug substance is chiral, it should be specified whether specific stereoisomer's or a mixture of stereoisomer's have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

	The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. A tabulated summary of the data can be provided.
2.3.S.4	**Control of Drug Substance (name, manufacturer)** A brief summary of justification of the specification(s), analytical procedures, and validation should be included. Specification from 3.2.S.4.1 should be provided. A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.
2.3.S.5	**Reference Standards or Materials (name, manufacturer)** Information from 3.2.S.5 should be included.
2.3.S.6	**Container Closure System (name, manufacturer)** A brief description and discussion of the information, from 3.2.S.6 should be included.
2.3.S.7	**Stability (name, manufacturer)** This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life,

	where relevant. The post-approval stability protocol overview should be included. A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.
2.3.P	**SUMMARY OF DRUG PRODUCT**
2.3.P.1	**Description and Composition of the Drug Product (name, dosage form)** Composition from 3.2.P.1 should be provided.
2.3.P.2	**Pharmaceutical Development (name, dosage form)** A brief discussion of the information and data from 3.2.P.2 should be presented. A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.
2.3.P.3	**Manufacture (name, dosage form)** A summary from 3.2.P.3 should include: ▪ Information on the manufacturer. ▪ A flow diagram, as provided under 3.2.P.3.3. A brief description of the ▪ manufacturing process and the controls ▪ process validation and/or evaluation

2.3.P.4	**Control of Excipients (name, dosage form)** A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.
2.3.P.5	**Control of Drug Product (name, dosage form)** A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided. Specification(s) from 3.2.P.5.1 should be provided. A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.
2.3.P.6	**Reference Standards or Materials (name, dosage form)** Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.
2.3.P.7	**Container Closure System (name, dosage form)** A brief description and discussion of the information in 3.2.P.7 should be included.
2.3.P.8	**Stability (name, dosage form)** A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with

	respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given. A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included. The post-approval stability protocol overview should be provided.
2.3.A	**APPENDICES** A summary of facility, equipment and excipients information described and appended under subsections of 3.2.A should be included
2.4	**NONCLINICAL OVERVIEW**
Nonclinical overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicological evaluation of the pharmaceutical. In general, it should address the interpretation of data, the clinical relevance of findings, cross-linking with quality aspects of the pharmaceutical, and the implications of nonclinical findings for the safe use of the pharmaceutical. The implications of any differences (e.g. chirality, chemical form, and impurity profile) between the compound used in the nonclinical studies and the product to be marketed should be discussed. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidelines.	

The section should contain appropriate reference citations to the Tabulated Summaries.

Where relevant guidelines on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidelines should be discussed and justified.

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in physiology, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose-dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed.

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect /

phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

- animal species used
- numbers of animals used
- routes of administration employed
- dosages used
- duration of treatment or of the study
- Systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose.
- the effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed.

2.4.1	**Introduction and GLP statement** A brief introduction about the contents of this section and a comment on the GLP status of the studies submitted should be provided
2.4.2	**Overview of the Non Clinical Testing Strategy**
2.4.3	**Pharmacology**
2.4.4	**Pharmacokinetics**
2.4.5	**Toxicology**
2.4.6	**Integrated Overview and Conclusions** This section should clearly define the characteristics of

	human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labelling).
2.4.7	**List of Literature References**
2.5	**CLINICAL OVERVIEW**

General Aspects

The section is intended to provide a critical analysis of the clinical data in the CTD. The clinical overview should primarily present the conclusions and implications of clinical summary (section 2.7) and individual clinical study reports (Module 5), and should not recapitulate them and cross-referencing for greater details is encouraged.

This section 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.

In order to achieve these objectives the clinical overview should:

- 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.
- Provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent endpoints, or on use in combination therapy).
- Provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimise benefits and manage risks.
- Address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved.
- Explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them.
- Explain the basis for important or unusual aspects of the prescribing information.

The length of this section will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for briefness and to facilitate understanding.

2.5.1	**Product Development Rationale** The discussion of the rationale for the development of the medicinal product should: • Identify the pharmacological class of the medicinal

	product. • Describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose (the targeted indication). • Briefly summarise the scientific background that supported investigation of the medicinal product for the indication(s) that was (were) studied. • Briefly describe the clinical development programme of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme. Briefly describe plans for the use of foreign clinical data. • Note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies. Pertinent published literature should be referenced. Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented.
2.5.2	**Overview of Biopharmaceutics** The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the

	to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).
2.5.3.	**Overview of Clinical Pharmacology** The purpose of this section is to present a critical analysis of the pharmacokinetic (PK), pharmacodynamic (PD), and related *in vitro* data in the CTD. The analysis should consider all relevant data and explain why and how the data support the conclusions drawn. It should emphasise unusual results and known or potential problems, or note the lack thereof. This section should address: ▪ pharmacokinetics, e.g., comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other medicinal products or other substances. ▪ Pharmacodynamics, e.g., information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favourable and

	unfavourable pharmacodynamic effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other medicinal products or substances; and possible genetic differences in response. ▪ Interpretation of the results and implications of immunogenicity studies, or other drug class specific PD studies summarised in *Section 2.7.2.4* of the Clinical Summary.
2.5.4	**Overview of Efficacy** The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered. The following issues should generally be considered: ▪ Relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any

	important patient populations excluded from critical studies, and participation of children and elderly. Differences between the studied population(s) and the population that would be expected to receive the medicinal product after marketing should be discussed. ▪ Implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified. Validation of any scales used should be discussed. ▪ For non-inferiority trials used to demonstrate efficacy, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of non-inferiority margin. ▪ statistical methods and any issues that could affect the interpretation of the study results (e.g., important modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol; support for any unplanned analyses; procedures for handling missing data; and corrections for multiple endpoints). ▪ Similarities and differences in results among studies, or in different patient sub-groups within

	studies, and their effect upon the interpretation of the efficacy data. ▪ Observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups. ▪ Support for the applicability to the new region of data generated in another region, where appropriate. ▪ For products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered. ▪ Data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range. ▪ The clinical relevance of the magnitude of the observed effects. ▪ If surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations. ▪ Efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.
2.5.5	**Overview of Safety** The purpose of this section is to provide a concise

	critical analysis of the safety data, noting how results support and justify proposed prescribing information. A critical analysis of safety should consider: ▪ Adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described. ▪ Special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation). ▪ Relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered. ▪ The nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database, e.g., related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. ▪ Common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are

	known to occur in active controls or other members of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest. ▪ Serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered. ▪ Similarities and differences in results among studies, and their effect upon the interpretation of the safety data. ▪ Any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism. ▪ Relation of adverse events to dose, dose regimen, and treatment duration.

	▪ Long-term safety. ▪ Methods to prevent, mitigate, or manage adverse events. ▪ Reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues. ▪ World-wide marketing experience. The following should be briefly discussed: - the extent of the world-wide experience, - any new or different safety issues identified, - Any regulatory actions related to safety. ▪ Support for the applicability to the new region of data generated in another region, where appropriate.
2.5.6	**Benefits and Risks Conclusions** The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceutics, clinical pharmacology, efficacy and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the medicinal product as they compare to available alternative treatments or to no treatment in illnesses

	where no treatment may be a medically acceptable option; and should clarify the expected place of the medicinal product in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here. This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class. This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points: ▪ The efficacy of the medicinal product for each proposed indication. ▪ Significant safety findings and any measures that may enhance safety. ▪ Dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens. ▪ Efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms. ▪ Data in children in different age groups, if applicable, and any plans for a development

	programme in children. ▪ Any risks to the patient of known and potential interactions, including food-drug and drug-drug interactions, and recommendations for product use. ▪ any potential effect of the medicinal product that might affect ability to drive or operate heavy machinery. Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include: ▪ the drug is for treatment of a non-fatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, pro-arrhythmic potential (effect on QT interval), or suggestion of heapatotoxicity. ▪ the proposed use is based on a surrogate endpoint and there is a well-documented important toxicity. ▪ safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training.
2.5.7	**Literature References** A list of references used should be provided. Copies of all references cited in the clinical overview should be provided in Section 5.4 of Module 5.
2.6	**NONCLINICAL WRITTEN AND TABULATED**

	SUMMARIES The primary purpose of the nonclinical written and tabulated summaries should be to provide a comprehensive factual synopsis of the nonclinical data.

GENERAL ASPECTS:

This part of guidelines is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics, and toxicology written & tabulated summaries in an acceptable format. However, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Nonclinical Written Summaries

- Whenever appropriate, age- and gender-related effects should be discussed. Consistent use of units throughout the summaries is recommended. A table for converting units might also be useful.
- 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.

General Presentation Issues

Order of presentation of information within sections,

- When available, *in vitro* studies should precede *in vivo* studies.
- Where multiple studies of the same type need to be summarised within the pharmacokinetics and toxicology sections, studies should be ordered by species, by route, and

then by duration (shortest duration first).

- Species should be ordered as follows: Mouse → Rat → Hamster → Other rodent → Rabbit → Dog → Non-human primate → Other non-rodent mammal and Non-mammals
- Routes of administration should be ordered as follows : The intended route for human use → Oral → Intravenous → Intramuscular → Intraperitoneal → Subcutaneous → Inhalation → Topical and to end with Others.

Use of Tables and Figures

- 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.
- To allow authors flexibility in defining the optimal structure for the written summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the nonclinical written summaries.
- Throughout the text, reference citations to the tabulated summaries should be included, in the following format: (Table X.X, Study/Report Number).

Nonclinical Tabulated Summaries

- One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.
- It is the responsibility of the applicant to decide on the best possible format for presentation of the data for each product.

	Presentation of the data in the best formats should ensure that a sufficient level of detail is available to the reviewer and should provide concise and accurate overviews of related information.
2.6.1	**Introduction** The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered: ▪ Brief information concerning the pharmaceutical's structure and pharmacologic properties. ▪ Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use.
2.6.2	**Written Summary of Pharmacology**
2.6.2.1	*Brief Summary* The principal findings from the pharmacology studies should be briefly summarized.
2.6.2.2	*Primary Pharmacodynamics* Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target are primary pharmacodynamic studies. Studies should be summarised and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

2.6.2.3	*Secondary Pharmacodynamics* Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target are secondary pharmacodynamic studies (these have sometimes been referred to as part of general pharmacology studies). Studies on should be summarised by organ system, where appropriate, and evaluated in this section.
2.6.2.4	*Safety Pharmacology* Safety pharmacology studies are defined as those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above. Studies should be summarised and evaluated in this section. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in humans. In such cases, these secondary pharmacodynamic studies should be considered along with safety pharmacology studies.
2.6.2.5	*Pharmacodynamic Drug Interactions* If they have been performed, pharmacodynamic drug interaction studies should be briefly summarised in this section.
2.6.2.6	*Discussion and Conclusions*

	This section provides an opportunity to discuss the pharmacologic evaluation and to consider the significance of any issues that arise.
2.6.2.7	*Tables and Figures* Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary under this subsection.
2.6.3	**Tabulated Summary of Pharmacology**
2.6.4	**Written Summary of Pharmacokinetics**
2.6.4.1	*Brief Summary* The principal findings from the pharmacokinetics studies should be briefly summarized. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasising, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.
2.6.4.2	*Methods of Analysis* This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of

	different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.
2.6.4.3	*Absorption* The following data should be summarised in this section: ▪ Absorption (extent and rate of absorption, *in vivo* and *in situ* studies) ▪ Kinetic parameters, bioequivalence and/or bioavailability (serum /plasma /blood PK studies)
2.6.4.4	*Distribution* The following data should be summarised in this section: ▪ Tissue distribution studies ▪ Protein binding and distribution in blood cells ▪ Placental transfer studies
2.6.4.5	*Metabolism (interspecies comparison)* The following data should be summarised in this section: ▪ Chemical structures and quantities of metabolites in biological samples ▪ Possible metabolic pathways ▪ Pre-systemic metabolism (Gastro-intestinal /hepatic first-pass effects) ▪ *In vitro* metabolism including P450 studies ▪ Enzyme induction and inhibition

2.6.4.6	*Excretion* The following data should be summarised in this section: ▪ Routes and extent of excretion ▪ Excretion in milk
2.6.4.7	*Pharmacokinetic Drug Interactions* If they have been performed, nonclinical pharmacokinetic drug-interaction studies (*in vitro* and/or *in vivo*) should be briefly summarised in this section.
2.6.4.8	*Other Pharmacokinetic Studies* If studies have been performed in nonclinical models of disease (e.g., renally impaired animals), they should be summarised in this section.
2.6.4.9	*Discussion and Conclusions* This section provides an opportunity to discuss the pharmacokinetic evaluation and to consider the significance of any issues that arise.
2.6.4.10	*Tables and Figures* Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary under this subsection.
2.6.5	**Tabulated Summary of Pharmacokinetics**

<table>
<tr><td>2.6.6</td><td>Written Summary of Toxicology</td></tr>
<tr><td>2.6.6.1</td><td>Brief Summary
The principal findings from the toxicology studies should be briefly summarized. In this section, the extent of the toxicological evaluation can be indicated by the use of a table listing of principal toxicological studies (results should not be presented in this table), for example:
<table>
<tr><th>Study type and duration</th><th>Route of administration</th><th>Species</th><th>Compound administered*</th></tr>
<tr><td>Single-dose toxicity</td><td>po and iv</td><td>Rat and mouse</td><td>Parent drug</td></tr>
<tr><td>Single-dose toxicity</td><td>po and iv</td><td>Rat and mouse</td><td>Metabolite X</td></tr>
<tr><td>Repeat-dose toxicity</td><td></td><td></td><td></td></tr>
<tr><td>1 month</td><td>po</td><td>Rat and dog</td><td>Parent drug</td></tr>
<tr><td>6 months</td><td>po</td><td>Rat</td><td>“ “</td></tr>
<tr><td>9 months etc.</td><td>po</td><td>Dog</td><td>“ “</td></tr>
</table>
* This column required only if metabolite(s) are investigated.
The scope of the toxicological evaluation should be described in relation to the proposed clinical use.</td></tr>
<tr><td>2.6.6.2</td><td>Single-Dose Toxicity
The single-dose data should be very briefly summarised, in order by species, by route. In some instances, it may be helpful to provide the data in the form of a table.</td></tr>
<tr><td>2.6.6.3</td><td>Repeat-Dose Toxicity (including supportive toxicokinetics evaluation)
Studies should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g.,</td></tr>
</table>

	nature and severity of target organ toxicity, dose (exposure)/response relationships, no observed adverse effect levels, etc.). Non-pivotal studies can be summarized in less detail (pivotal studies are the definitive GLP studies specified by ICH Guideline M3).
2.6.6.4	*Genotoxicity* Studies should be briefly summarised in the following order: ▪ *in vitro* non-mammalian cell system ▪ *in vitro* mammalian cell system ▪ *in vivo* mammalian system (including supportive toxicokinetics evaluation) ▪ other systems
2.6.6.5	*Carcinogenicity (including supportive toxicokinetics evaluations)* A brief rationale should explain why the studies were chosen and the basis for high-dose selection. Individual studies should be summarised in the following order: ▪ Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics) ▪ Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

	▪ Other studies
2.6.6.6	*Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations)* Studies should be summarised in the following order, giving brief details of the methodology and highlighting important findings: ▪ Fertility and early embryonic development ▪ Embryo-fetal development ▪ Prenatal and postnatal development, including maternal function ▪ Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted. If modified study designs are used, the sub-headings should be modified accordingly. Male fertility study should be summarized
2.6.6.7	*Local Tolerance* If local tolerance studies have been performed, they should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings.
2.6.6.8	*Other Toxicity Studies (if available)* If other studies have been performed, they should be summarised. When appropriate, the rationale for conducting the studies should be provided.

	▪ Antigenicity ▪ Immunotoxicity ▪ Mechanistic studies (if not reported elsewhere) ▪ Dependence ▪ Studies on metabolites ▪ Studies on impurities ▪ Other studies
2.6.6.9	*Discussion and Conclusions* This section should provide an opportunity to discuss the toxicological evaluation and the significance of any issues that arise. Tables or figures summarizing this information are recommended.
2.6.6.10	*Tables and Figures* Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary under this subsection.
2.6.7	**Tabulated Summary of Toxicology**
2.7	**CLINICAL SUMMARY**
This section is intended to provide a detailed, factual summarization of all of the clinical information in the CTD. This includes information provided in clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document	

should focus on factual observations. The length of the summary will vary substantially according to the information to be conveyed.	
2.7.1	**Summary of Biopharmaceutic Studies and Associated Analytical Methods**
2.7.1.1	*Background and Overview* This section should provide the reviewer with an overall view of the formulation development process, the *in vitro* and *in vivo* dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and *in vitro* dissolution profile database.
2.7.1.2	*Summary of Results of Individual Studies* A tabular listing of all biopharmaceutical studies should generally be provided, together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important *in vitro* or *in vivo* data and information relevant to BA and BE. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. These narratives may be abstracted from the clinical study report synopsis. References to the full report of each study should be included in the narratives.

2.7.1.3	*Comparison and Analyses of Results Across Studies* This section should provide a factual summary of all *in vitro* dissolution, BA, and comparative BA studies carried out with the drug substance or drug product, with particular attention to differences in results across studies. This overview should typically summarise the findings in text and tables.
2.7.1.4	*Appendix* Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section. Tables related to bioavailability and *in vitro* dissolution studies may contain study ID, objectives, study design, results and location of detailed reports in the application. Applicants should decide whether information and results from these studies are best presented in tables, text or figures in order to aid clarity.
2.7.2	**Summary of Clinical Pharmacology Studies**
2.7.2.1	*Background and Overview* This section should provide the reviewer with an overall view of the clinical pharmacology studies. These studies include clinical studies performed to evaluate human PK, and PD, and *in vitro* studies performed with human cells, tissues, or related materials (hereinafter referred to

	as human biomaterials) that are pertinent to PK processes. This section should not include detailed information about individual studies.
2.7.2.2	*Summary of Results of Individual Studies* A tabular listing of all clinical pharmacology studies should generally be provided, together with a narrative description of the relevant features and outcomes of each of the critical individual studies that provided *in vitro* or *in vivo* data and information relevant to PK, PD and PK/PD relationships. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. References to full report of each study should be included in the narratives. Summaries of dose-response or concentration response (PK/PD) studies with pharmacodynamic endpoints should generally be included in this section. In some cases, however, when well-controlled dose-response PD or PK/PD studies provide important evidence of efficacy or safety, they should be placed in 2.7.3 or 2.7.4 as appropriate and referenced, but not summarised, here.
2.7.2.3	*Comparison and Analyses of Results Across Studies* This section should use the results of all *in vitro* human biomaterial studies and PK, PD and PK/PD studies to

	characterise the PK, PD and PK/PD relationships of the drug. Results related to the inter- and intra-individual variability in these data and the intrinsic and extrinsic factors affecting these pharmacokinetic relationships should be discussed.
2.7.2.4	*Special Studies* This section should include studies that provide special types of data relevant to specific types of medicinal products. For example, immunogenicity studies, susceptibility studies for a antibiotic that are not part of efficacy data
2.7.2.5	*Appendix* Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section. Applicants should also decide whether information and results from clinical pharmacology studies are best presented in tables, text or figures in order to aid clarity. If, for example, results are best presented in text and figures, the tables might simply list the studies. In designing tables, if any, for various types of other clinical pharmacology studies such as those listed below, applicants should consider including the following types of information. These examples are for illustrative purposes only and the sponsor should decide which information needs to be presented.

	▪ Metabolism studies using human biomaterials: biomaterials used (e.g., microsomes, hepatocytes), probe drugs, enzymatic pathways and % contribution and relevant kinetic parameters (e.g., Vmax, Km). ▪ *In vitro* studies of drug-drug interactions using human biomaterials: for studies of other drugs inhibiting the new drug, the metabolite(s) inhibited, enzymatic pathways affected, range of inhibitor concentrations used, IC_{50} and K_i values and proposed mechanism of inhibition should be included. For studies of the new drug inhibiting other drugs, the drugs and metabolites inhibited should be included, along with the information mentioned above. ▪ Population PK studies: co-variates studied, number and type of subjects or patients studied, summary statistical parameters and final estimates of mean (± standard deviation) PK parameters.
2.7.3	**Summary of Clinical Efficacy** A separate Section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.7.3 is submitted, the sections should be labelled 2.7.3 pneumonia, 2.7.3 URI, etc.
2.7.3.1	*Background and Overview of Clinical Efficacy* This section should describe the program of controlled

	studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought. Any results of these studies that are pertinent to evaluation of safety should be discussed in Section 2.7.4, Summary of Clinical Safety.
2.7.3.2	*Summary of Results of Individual Studies* A tabular listing of all studies that provided (or were designed to provide) information relevant to product efficacy should generally be provided, together with narrative descriptions for important studies. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. These narratives can be abstracted from the synopses of the clinical study reports. References to the full report of each study should be included in the narratives.
2.7.3.3	*Comparison and Analyses of Results Across Studies* Using text, figures, and tables as appropriate, the subsections of 2.7.3.3 should summarise all available data that characterise the efficacy of the drug. This summary should include analyses of all data, irrespective of their support for the overall conclusion and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce

	each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified. The section will generally utilise two kinds of analyses: comparison of results of individual studies, and analysis of data combined from various studies. Details of analyses that are too extensive to be reported in a summary document should be presented in a separate report, to be placed in Module 5.
2.7.3.3.1	*Study Populations* The demographic and other baseline characteristics of patients across all efficacy studies should be described. Tabular presentations that combine and compare study populations across studies may be useful.
2.7.3.3.2	*Comparison of Efficacy Results of all Studies* The results of any bridging studies using clinical endpoints should be summarised here. The results from all studies designed to evaluate the drug's efficacy should be summarised and compared, including studies with inconclusive or negative results. Important differences in study design such as endpoints, control group, study duration, statistical methods, patient population, and dose should be identified. Comparisons of results across studies should focus on pre-specified primary endpoints. However, when the primary endpoints involved different variables or time

	points in different efficacy studies, it may be useful to provide cross-study comparisons of important data elements that were obtained in all studies. If results over time are important, results of studies may be displayed in a figure that illustrates the change over time in each study. If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to a predefined protocol or is a post hoc exercise. Any differences in trial designs or populations or in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions. A detailed description of the methodology and results of the meta-analysis should generally be submitted in a separate report under Module 5.
2.7.3.3.3	*Comparison of Results in Sub-populations* The results of individual studies or overview analyses of efficacy in specific populations should be summarised in this section. The purpose of these comparisons should be to show whether the claimed treatment effects are observed consistently across all relevant sub-populations, especially those where there are special reasons for concern. The comparisons may highlight apparent variations in efficacy that require further investigation and discussion. The limitations of such analyses, however, should be recognised, and it is

	important to note that their purpose is not to provide the basis for specific claims, nor to attempt to improve the evidence of efficacy in situations where the overall results are disappointing. Given the limited sample sizes in individual studies, analyses across multiple studies should be performed to evaluate effects of major demographic factors (age, sex, and race) and of other predefined or relevant intrinsic and extrinsic factors (e.g., disease severity, prior treatment, concomitant illness, concomitant drugs, alcohol, tobacco, and body weight) on efficacy. Factors of special interest may arise from general concerns (e.g., the elderly) or from specific issues that are related to the pharmacology of the drug or that have arisen during earlier drug development. Efficacy in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Depending on the data set, if extensive, detailed efficacy analyses are performed, they can be placed in Module 5, with the results of those analyses reported here.
2.7.3.4	*Analysis of Clinical Information Relevant to Dosing Recommendations* This section should provide an integrated summary and analysis of all data that pertain to the dose-response or blood level-response relationships of effectiveness (including dose-blood level relationships), and thus have contributed to dose selection and choice of dose interval.

	Relevant data from nonclinical studies may be referenced and relevant data from PK studies, other clinical pharmacology studies, and controlled and uncontrolled clinical studies should be summarised to illustrate these dose-response or blood level-response relationships. While the interpretation of how these data support specific dosing recommendations should be supplied in the Clinical Overview document, the individual study results and any cross-study analyses that will be used to support the dosing recommendations (including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualisation of dosage) should be summarised here.
2.7.3.5	*Persistence of Efficacy and/or Tolerance Effects* Available information on persistence of efficacy over time should be summarised. The number of patients for whom long-term efficacy data are available, and the length of exposure, should be provided. Any evidence of tolerance (loss of therapeutic effects over time) should be noted.
2.7.3.6	*Appendix* Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the Section. Tables should identify all studies pertinent to the

	evaluation of efficacy (including studies that were terminated or are not yet completed, studies that failed to show effectiveness for any reason, studies available only as publications, studies reported in full technical reports, and studies described in abbreviated reports); and should provide the most important results of those studies.
2.7.4	**Summary of Clinical Safety** This section should be a summary of data relevant to safety in the intended patient population, integrating the results of individual clinical study reports as well as other relevant reports, e.g., the integrated analyses of safety that are routinely submitted in some regions. The display of safety-related data can be considered at three levels: ▪ The extent of exposure (dose, duration, number of patients, type of patients) should be examined to determine the degree to which safety can be assessed from the database. ▪ The more common adverse events and changes in laboratory tests should be identified and classified, and their occurrence should be summarised. ▪ Serious adverse events and other significant adverse events should be identified and their occurrence should be summarised. The safety profile of the drug, described on the basis of analysis of all clinical safety data, should be outlined in

	a detailed, clear, and objective manner, with use of tables and figures.
2.7.4.1	*Exposure to the Drug*
2.7.4.1.1	*Overall Safety Evaluation Plan and Narratives of Safety Studies* The overall safety evaluation plan should be described briefly, including special considerations and observations concerning the nonclinical data, any relevant pharmacological class effects, and the sources of the safety data (controlled trials, open studies, etc). A tabular listing of all clinical studies that provided safety data, grouped appropriately, should generally be provided. Narrative descriptions of these studies should be provided here, except that narrative descriptions for studies that contributed both efficacy and safety data should be included in *Section 2.7.3.2* and cross-referenced here. The narratives should provide enough detail to allow the reviewer to understand the exposure of study subjects to the test drug or control agent, and how safety data were collected (including the methods used and the extent of safety monitoring of the subjects enrolled in the individual studies). If some studies are not analysed separately but are grouped for safety analysis, that should be noted, and a single narrative description can be provided.
2.7.4.1.2	*Overall Extent of Exposure*

	A table and appropriate text should be generated to summarise the overall extent of drug exposure from all phases of the clinical study development programme. The table should indicate the numbers of subjects exposed in studies of different types and at various doses, routes and durations. It is assumed that all subjects who were enrolled and received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided. A summary table should provide the reader with an overview of the demographic characteristics of the population that was exposed to the therapeutic agent during its development.
2.7.4.2	*Adverse Events*
2.7.4.2.1	*Analysis of Adverse Events* Data on the frequency of adverse events should be described in text and tables. Text should appear in the appropriate subsections of *Section 2.7.4.2.1* and the tables that are not embedded in the text should be placed in the *Section 2.7.4.7* Appendix. All adverse events occurring or worsening after treatment has begun should be summarised in tables listing each event, the number of subjects in whom the event occurred and the frequency of occurrence in subjects treated with the drug under investigation, with comparator drugs and with placebo. Such tables could

	also present results for each dose and could be modified to show, e.g., adverse event rates by severity, by time from onset of therapy, or by assessment of causality. When most of the relevant safety data are derived from a small number of studies (e.g., one or two studies), or when very different study subject populations were enrolled in the studies that were performed, presentation of data by study will often be appropriate. When the relevant exposure data is not concentrated in a small number of studies, however, grouping the studies and pooling the results to improve precision of estimates and sensitivity to differences should generally be considered. While often useful, pooling of safety data across studies should be approached with caution because in some cases interpretation can be difficult, and it can obscure real differences. In cases where differences are apparent, it is more appropriate to present the data by study. When a decision is made to pool data from several studies, the rationale for selecting the method used for pooling should be described. It is common to combine the numerator events and the denominators for the selected studies. If substantial differences are seen between clinical trials in the rates of adverse events, these differences should be noted and possible reasons should be discussed (e.g., relevant differences in study populations, in dose

	administration, or in methods of collecting adverse event data). Adverse events should be described as shown in the individual study report. In combining data from many studies, it is important to use standardised terms to describe events and collect synonymous terms under a single preferred term. Examination of which adverse events led to change in therapy (discontinuation of drug use, change in dose, need for added therapy) can help in assessing the clinical importance of adverse events. Overall discontinuation rates by study may be useful but it is also important to specify the particular adverse events leading to discontinuation in a separate table. The preferred terms should be grouped by body system and arranged by decreasing frequency.
2.7.4.2.1.1	*Common Adverse Events* Tabular displays of adverse event rates should be used to compare rates in treatment and control groups. For this analysis it may be helpful to combine the event severity categories and the causality categories, if they are used, leading to a simpler side-by-side comparison of treatment groups. It is usually useful to examine more closely the more common adverse events that seem to be drug related (e.g., those that show that a dose response and/or a clear difference between drug and placebo rates) for relationship to relevant factors, including dosage; mg/kg

	or mg/m^2 dose; dose regimen; duration of treatment; total dose; demographic characteristics such as age, sex, race; concomitant medication use; other baseline features such as renal status; efficacy outcomes; drug concentration, where available.
2.7.4.2.1.2	*Deaths* A table in the *Section 2.7.4.7* Appendix should list all deaths occurring while on study (including deaths that occurred shortly following treatment termination, e.g., within 30 days or as specified in the study protocol, as well as all other deaths that occurred later but may have resulted from a process that began during studies). Only deaths that are clearly disease-related per protocol definitions and not related to the investigational product, either in studies of conditions with high mortality such as advanced cancer or in studies where mortality from disease is a primary study endpoint, should be excepted from this listing. Even these deaths should be examined for any unexpected patterns between study arms, and further analysed if unexplained differences are observed. Deaths should be examined individually and analysed on the basis of rates in individual trials and appropriate pools of trials, considering both total mortality and cause-specific deaths. Potential relationships to the factors listed in *Section 2.7.4.2.1.1* should also be considered. Although cause-specific mortality can be difficult to determine,

	some deaths are relatively easy to interpret. Thus deaths due to causes expected in the patient population (heart attacks and sudden death in an angina population) are individually not considered to be informative, but even one death due to a QT interval prolongation-associated arrhythmia, aplastic anaemia, or liver injury may be informative. Special caution is appropriate before an unusual death is attributed to concomitant illness.
2.7.4.2.1.3	*Other Serious Adverse Events* Summaries of all serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be displayed. Serious adverse events that occurred after the drug use was discontinued should be included in this section. The display should include major laboratory abnormalities, abnormal vital signs, and abnormal physical observations that are considered serious adverse events. Results of analyses or assessments of serious adverse events across studies should be presented. Serious events should be examined for frequency over time, particularly for drugs that may be used chronically. Potential relationships to the factors listed in *Section 2.7.4.2.1.1* should also be considered.
2.7.4.2.1.4	*Other Significant Adverse Events* Marked haematological and other laboratory abnormalities (other than those meeting the definition of

	serious) and any events that led to a substantial intervention (premature discontinuation of study drug, dose reduction, or substantial additional concomitant therapy), other than those reported as serious adverse events, should be displayed. In addition, the study data should be examined for any potential relationships to the factors listed in *Section 2.7.4.2.1.1*.
2.7.4.2.1.5	*Analysis of Adverse Events by Organ System or Syndrome* It is generally useful to summarise adverse events by organ system so that they may be considered in the context of potentially related events including laboratory abnormalities. Such presentations of adverse events by organ system should be placed in this section and titled by the organ system under consideration. The list of organ systems to be addressed and the approach to grouping certain events should be selected as appropriate to best present the adverse event data for the medicinal product. If some adverse events tend to occur in syndromes (e.g., influenza-like syndrome, cytokine release syndrome), the applicant may choose to by syndromes rather than organ systems.
2.7.4.2.2	*Narratives* The locations in the application of individual narratives of patient deaths, other serious adverse events, and other significant adverse events deemed to be of special

	interest because of clinical importance should be referenced here for the convenience of the reviewer. The narratives themselves should be a part of the individual study reports, if there is such a report. In cases where there is no individual study report (e.g., if many open studies are pooled as part of a safety analysis and are not individually described), narratives can be placed in Module 5, *Section 5.3.5.3*. Narratives should not be included here, unless an abbreviated narrative of particular events is considered critical to the summary assessment of the drug.
2.7.4.3	*Clinical Laboratory Evaluations* This section should describe changes in patterns of laboratory tests with drug use. Marked laboratory abnormalities and those that led to a substantial intervention should be reported in *Section 2.7.4.2.1.3 or 2.7.4.2.1.4*. If these data are also presented in this section, this duplicate reporting should be made clear for the reviewer. The appropriate evaluations of laboratory values will in part be determined by the results seen, but, in general, the analyses described below should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as compatible with study sizes. In addition, normal laboratory ranges should be given for each analysis. Where possible, laboratory values should be provided in standard

	international units. Laboratory data should include haematology, clinical chemistry, urinalysis and other data as appropriate.
2.7.4.4	*Vital Signs, Physical Findings, and Other Observations Related to Safety* The manner of presenting cross-study observations and comparisons of vital signs (e.g., heart rate, blood pressure, temperature, and respiratory rate), weight and other data (e.g., electrocardiograms, X-rays) related to safety should be similar to that for laboratory variables. If there is evidence of a drug effect, any dose-response or drug concentration-response relationship or relationship to individual variables (e.g., disease, demographics, and concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events. Particular attention should be given to studies that were designed to evaluate specific safety issues, e.g., studies of QT interval prolongation.
2.7.4.5	*Safety in Special Groups and Situations*
2.7.4.5.1	*Intrinsic Factors* This section should summarise safety data pertinent to individualising therapy or patient management on the basis of demographic and other factors defined as "intrinsic ethnic factors". These factors include age, sex, height, weight, lean body mass, genetic polymorphism,

	body composition, other illness and organ dysfunction. Safety in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Analysis of the impact of such factors on safety outcomes should have been presented in other sections but should be summarised here, together with pertinent PK or other information, e.g., in patients with renal or hepatic disease. If a sufficiently large number of subjects with a given co-morbid condition such as hypertension, heart disease, or diabetes were enrolled, analyses should be carried out to assess whether the co-morbid condition affected the safety of the drug under study. Cross reference should be made to the tables or description of adverse events when analyses of such sub-groups have been carried out.
2.7.4.5.2	*Extrinsic Factors* This section should summarise safety data pertinent to individualising therapy or patient management on the basis of factors defined as "extrinsic ethnic factors". These are factors associated with the patient environment. Examples are the medical environment, use of other drugs (see 2.7.4.5.3, Drug Interactions), use of tobacco, use of alcohol, and food habits. For example, if a potential interaction with alcohol is suggested by the metabolic profile, by the results of studies, by post-marketing experience, or by information

	on similar drugs, information should be provided here.
2.7.4.5.3	*Drug Interactions* Studies on potential drug-drug or drug-food interactions should be summarised in the Summary of Clinical Pharmacology Studies section of the CTD (Section 2.7.2). The potential impact on safety of such interactions should be summarised here, based on PK, PD, or clinical observations. Any observed changes in the adverse event profile, changes in blood levels thought to be associated with risk, or changes in drug effects associated with other therapy should be presented here.
2.7.4.5.4	*Use in Pregnancy and Lactation* Any information on safety of use during pregnancy or breast-feeding that becomes available during clinical development or from other sources should be summarised here.
2.7.4.5.5	*Overdose* All available clinical information relevant to overdose, including signs/symptoms, laboratory findings, and therapeutic measures/treatments and antidotes (if available) should be summarised and discussed. Information on the efficacy of specific antidotes and dialysis should be provided if available.
2.7.4.5.6	*Drug Abuse* Any relevant studies/information regarding the investigation of the dependence potential of a new

	therapeutic agent in animals and in humans should be summarised and cross-referenced to the nonclinical summary. Particularly susceptible patient populations should be identified.
2.7.4.5.7	*Withdrawal and Rebound* Any information or study results pertinent to rebound effects should be summarised. Events that occur, or increase in severity, after discontinuation of double-blind or active study medication should be examined to see if they are the result of withdrawal of the study medication. Particular emphasis should be given to studies designed to evaluate withdrawal and/or rebound. Data concerning tolerance should be summarised under *Section 2.7.3.5* in the Summary of Clinical Efficacy.
2.7.4.5.8	*Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability* Safety data related to any impairment in the senses, co-ordination, or other factor that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability should be summarised. This includes relevant adverse effects reported in safety monitoring (e.g., drowsiness) and specific studies concerning effects on ability to drive or operate machinery or impairment of mental ability.
2.7.4.6	*Post-marketing Data* If the drug has already been marketed, all relevant post-

	marketing data available to the applicant (published and unpublished, including periodic safety update reports if available) should be summarised. The periodic safety update reports can be included in Module 5. Details of the number of subjects estimated to have been exposed should be provided and categorised, as appropriate, by indication, dosage, route, treatment duration, and geographic location. The methodology used to estimate the number of subjects exposed should be described. If estimates of the demographic details are available from any source, these should be provided. A tabulation of serious events reported after the drug is marketed should be provided, including any potentially serious drug interactions. Any post-marketing findings in subgroups should be described.
2.7.4.7	*Appendix* Tabular presentations should be provided that summarise the important results from all studies pertinent to the evaluation of safety and particularly to support product labelling. Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document, however, lengthy tables are provided here.
2.7.5	**Literature References** A list of references cited in the Clinical Summary should

	be provided. Copies of all important references should be provided in Module 5, Section 5.4. The reference list should indicate which references are available in Module 5, Section 5.4. All references that have not been provided should be available upon request.
2.7.6	**Synopses of Individual Studies** This section should include the table entitled Listing of Clinical Studies, described in guidance for Module 5, followed by all individual study synopses organised in the same sequence as the study reports in Module 5. It is expected that one synopsis will be prepared per study and that the same synopsis will be included in the clinical study report in Module 5. The length of a synopsis will usually be up to 3 pages, but a synopsis for a more complex and important studies may be longer. Within the individual synopsis, tables and figures should be used as appropriate to aid clarity.

6.4 MODULE 3: QUALITY

MODULE 3: QUALITY	
3.1	**TABLE OF CONTENTS OF MODULE 3**
3.2	**BODY OF DATA**
3.2.S	**DRUG SUBSTANCE(S)** NOTE: For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance. If the applicant has a manufacturing permission for bulk drug(s)/ Drug substance /API, please provide a copy of the same and further details under drug substance can be concise as the same would have already submitted in great details to this office at the time of request for approval of drug substance. Otherwise, provide complete details as below.
3.2.S.1	**General information (name, manufacturer)**
3.2.S.1.1	*Nomenclature (name, manufacturer)* Information on the nomenclature of drug substance should be provided. For example: ▪ Recommended International Non-proprietary Name (INN); ▪ Compendial name if relevant

	▪ Chemical name(s) ▪ Company or laboratory code ▪ Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), British Approved Name (BAN), etc. ▪ Chemical Abstracts Service (CAS) registry number
3.2.S.1.2	*Structure (name, manufacturer)* The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. (As applicable)
3.2.S.1.3	*General Properties (name, manufacturer)* A list should be provided of physicochemical and other relevant properties of the drug substance.
3.2.S.2	**Manufacture of Drug Substance (name, manufacturer)**
3.2.S.2.1	*Manufacturer(s) (name, manufacturer)* The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.
3.2.S.2.2	*Description of Manufacturing Process and Process Controls (name, manufacturer)* A sequential procedural narrative of the manufacturing process should be submitted. The narrative should

	include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time). A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents. Alternate processes should also be explained. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5
3.2.S.2.3	*Control of Materials (name, manufacturer)* 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. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate.
3.2.S.2.4	*Controls of Critical Steps and Intermediates (name,*

	manufacturer) Critical Steps: Tests and acceptance criteria performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure the controlled process should be provided. Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.
3.2.S.2.5	*Process Validation and/or Evaluation (name, manufacturer)* Process validation and/or evaluation studies for aseptic processing and sterilisation should be included.
3.2.S.2.6	*Manufacturing Process Development (name, manufacturer)* A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot and, if available, production scale batches.
3.2.S.3	**Characterization of Drug Substance (name, manufacturer)**
3.2.S.3.1	*Elucidation of Structure and other Characteristics (name, manufacturer)* Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information

	such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.
3.2.S.3.2	*Impurities (name, manufacturer)* Information on impurities should be provided.
3.2.S.4	**Quality control of Drug Substance (name, manufacturer)**
3.2.S.4.1	*Specification and Justification of Specification (name, manufacturer)* The specification for the drug substance and the justification for the drug substance specification should be provided.
3.2.S.4.2	*Analytical Procedures (name, manufacturer)* The analytical procedures used for testing the drug substance should be provided.
3.2.S.4.3	*Validation of Analytical Procedures (name, manufacturer)* Analytical validation information for the analytical procedures used for testing the drug substance should be provided.
3.2.S.4.4	*Batch Analyses (name, manufacturer)* Description of batches and results of batch analyses should be provided.
3.2.S.5	**Reference Standards or Materials (name, manufacturer)**

	Information on the reference standards or reference materials used for testing of the drug substance should be provided.
3.2.S.6	**Container Closure System (name, manufacturer)** A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. The suitability should be discussed with respect to choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.
3.2.S.7	**Stability of Drug Substance (name, manufacturer)**
3.2.S.7.1	*Stability Summary and Conclusions (name, manufacturer)* The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.
3.2.S.7.2	*Post-approval Stability Protocol and Stability Commitment (name, manufacturer)*

	The post-approval stability protocol and stability commitment should be provided.
3.2.S.7.3	*Stability Data (name, manufacturer)* Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative. Information on analytical procedures used to generate data and validation of these procedures should be included.
3.2.P	**DRUG PRODUCT (NAME, DOSAGE FORM)**
3.2.P.1	**Description and Composition of the Drug Product (name, dosage form)** A description of the drug product and its composition should be provided. The information provided should include, for example: ▪ Description of the dosage form. For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should also be provided. ▪ Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), 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), if any, and

	▪ Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.
3.2.P.2	**Pharmaceutical Development (name, dosage form)** This 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 that are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.
3.2.P.2.1	*Components of the Drug Product (name, dosage form)*
3.2.P.2.1.1	*Drug Substance (name, dosage form)* The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. For combination products, the compatibility of drug substances with each

	other should be discussed.
3.2.P.2.1.2	*Excipients (name, dosage form)* The choice of excipients listed in 3.2.P.1, their concentration, and their characteristics that can influence the drug product performance should be discussed relative to their respective functions.
3.2.P.2.2	*Drug Product (name, dosage form)*
3.2.P.2.2.1	*Formulation Development (name, dosage form)* A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage.
3.2.P.2.2.2	*Overages (name, dosage form)* Any overages in the formulation(s) described in 3.2.P.1 should be justified.
3.2.P.2.2.3	*Physicochemical and Biological Properties (name, dosage form)* Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, potency and/or immunological activity, should be addressed.
3.2.P.2.3	*Manufacturing Process Development (name, dosage form)* The selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular its critical

	aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified. Differences between the manufacturing process (es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.
3.2.P.2.4	*Container Closure System (name, dosage form)* The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).
3.2.P.2.5	*Microbiological Attributes (name, dosage form)* Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to

	prevent microbial contamination should be addressed.
3.2.P.2.6	*Compatibility (name, dosage form)* The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed.
3.2.P.3	**Manufacture of Drug Product (name, dosage form)**
3.2.P.3.1	*Manufacturer(s) (name, dosage form)* The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.
3.2.P.3.2	*Batch Formula (name, dosage form)* A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.
3.2.P.3.3	*Description of Manufacturing Process and Process Controls (name, dosage form)* A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

	A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant. Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated. Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section.
3.2.P.3.4	*Controls of Critical Steps and Intermediates (name, dosage form)* Critical Steps: Tests performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process to ensure that the process is controlled and acceptance criteria should be provided. Intermediates: Information on the quality and control of

	intermediates isolated during the process should be provided.
3.2.P.3.5	*Process Validation and/or Evaluation (name, dosage form)* Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.
3.2.P.4	**Control of Excipients (name, dosage form)**
3.2.P.4.1	*Specifications and Justification of Specifications (name, dosage form)* The specifications for excipients and justifications for the proposed specifications should be provided.
3.2.P.4.2	*Analytical Procedures (name, dosage form)* The analytical procedures used for testing the excipients should be provided, where appropriate.
3.2.P.4.3	*Validation of Analytical Procedures (name, dosage form)* Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.
3.2.P.4.4	*Excipients of Human or Animal Origin (name, dosage form)*

	For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data).
3.2.P.4.5	*Excipients used for the first time (name, dosage form)* For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format.
3.2.P.5	**Control of Drug Product (name, dosage form)**
3.2.P.5.1	*Specification(s) and Justification of Specification(s) (name, dosage form)* The specification(s) for the drug product and justification for the proposed drug product specification(s) should be provided.
3.2.P.5.2	*Analytical Procedures (name, dosage form)* The analytical procedures used for testing the drug product should be provided.
3.2.P.5.3	*Validation of Analytical Procedures (name, dosage form)* Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.
3.2.P.5.4	*Batch Analyses (name, dosage form)*

	A description of batches and results of batch analyses should be provided.
3.2.P.5.5	*Characterisation of Impurities (name, dosage form)* Information on the characterisation of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".
3.2.P.6	**Reference Standards or Materials (name, dosage form)** Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".
3.2.P.7	**Container Closure System (name, dosage form)** A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate. For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

	Suitability information should be located in 3.2.P.2.
3.2.P.8	**Stability of drug product (name, dosage form)**
3.2.P.8.1	*Stability Summary and Conclusion (name, dosage form)* 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.
3.2.P.8.2	*Post-approval Stability Protocol and Stability Commitment (name, dosage form)* The post-approval stability protocol and stability commitment should be provided.
3.2.P.8.3	*Stability Data (name, dosage form)* Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included. Information on characterisation of impurities is located in 3.2.P.5.5.
3.2.A	**APPENDICES**
3.2.A.1	**Facilities and Equipment (name, manufacturer)** A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and

	out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product. A summary description of product-contact equipment and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate. Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the product manufacturing are performed.
3.2.A.2	**Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)**
3.2.A.3	**Excipients** Any documents/ appendices of excipients should be presented
3.3	**LITERATURE REFERENCES** Key literature referenced should be provided, if applicable.
Further Clarifications: ▪ There can be a number of instances where repeated sections	

can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the CTD-Q heading, for example, 2.3.S Drug Substance (Name, Manufacturer A).

- In some cases, information at Drug Product section has to be presented separately meaning one complete Drug Product section followed by other complete Drug Product sections. Example: A drug product supplied with a reconstitution diluent should be presented in separate Drug Product sections and it could be titled 3.2.P (Drug Product) and 3.2.P (Diluent).
- Appendices: If both drug substance and drug product information is included in the appendices, then the preferred presentation is drug substance first and then drug product within each section, for example, 3.2.A.1 (Drug Substance, then Drug Product), then 3.2.A.2 (Drug Substance, then Drug Product), then 3.2.A.3 (Drug Substance, if applicable, then Drug Product).

6.5 MODULE 4: NON-CLINICAL STUDY REPORTS

MODULE 4: NON-CLINICAL STUDY REPORTS	
4.1	**TABLE OF CONTENTS OF MODULE 4** Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the CTD.
4.2	**STUDY REPORTS**
4.2.1	**Pharmacology**
4.2.1.1	Primary Pharmacodynamics
4.2.1.2	Secondary Pharmacodynamics
4.2.1.3	Safety Pharmacology
4.2.1.4	Pharmacodynamic Drug Interactions
4.2.2	**Pharmacokinetics**
	Analytical Methods and Validation Reports (if separate reports are available) Absorption Distribution Metabolism Excretion Pharmacokinetic Drug Interactions (nonclinical) Other Pharmacokinetic Studies
4.2.3	**Toxicology**
4.2.3.1	Single-Dose Toxicity (in order by species, by route)

4.2.3.2	Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetic evaluations)
4.2.3.3	Genotoxicity *In vitro* study followed by *In vivo* (including supportive toxicokinetics evaluations)
4.2.3.4	Carcinogenicity (including supportive toxicokinetics evaluations) Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics) Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics) and any other study reports should be provided in this section.
4.2.3.5	Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations). For example, Male fertility study report, Female fertility and early embryonic development, Embryo-fetal development, Prenatal and postnatal development, including maternal function, Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, etc.
4.2.3.6	Local Tolerance
4.2.3.7	Other Toxicity Studies (if available), for example Antigenicity Immunotoxicity

	Mechanistic studies (if not included elsewhere) Dependence Metabolites Impurities Other
4.3	**LITERATURE REFERENCES**

CENTRAL DRUGS STANDARD CONTROL ORGANISATION
CDSCO CDSCO
MINISTRY OF HEALTH, GOVERNMENT OF INDIA

6.6 MODULE 5: CLINICAL STUDY REPORTS

MODULE 5: CLINICAL STUDY REPORTS	
▪ This section recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. ▪ Each study report should appear in ONLY one section. The placement of a report is determined by the primary objective of the study. When there are multiple objectives, the study should be cross-referenced in the various sections. ▪ An explanation such as "not applicable" or "no study conducted" should be provided when no report or information is available for a section or subsection.	
5.1	**TABLE OF CONTENTS OF MODULE 5**
5.2	**TABULAR LISTING OF ALL CLINICAL STUDIES** A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in **Annexure III**. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section 5.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.
5.3	**CLINICAL STUDY REPORTS**

5.3.1	**Reports of Biopharmaceutical Studies** BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or *in vitro* dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.
5.3.1.1	*Bioavailability (BA) Study Reports* BA studies in this section should include ▪ Studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form. ▪ Dosage form proportionality studies, and ▪ Food-effect studies.
5.3.1.2	*Comparative BA and Bioequivalence (BE) Study Reports* Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between ▪ the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, ▪ the drug product used in clinical studies supporting

	effectiveness and the drug product used in stability batches, and ▪ Similar drug products from different manufacturers.
5.3.1.3	*In Vitro – In Vivo Correlation Study Reports* *In vitro* dissolution studies that provide BA information, including studies used in seeking to correlate *in vitro* data with *in vivo* correlations, should be placed in this section.
5.3.1.4	*Reports of Bioanalytical and Analytical Methods for Human Studies* Bioanalytical and/or analytical methods for biopharmaceutic studies or *in vitro* dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in *Section 5.3.1.4* and referenced in the appropriate individual study reports.
5.3.2	**Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials** Human biomaterials is a term used to refer to proteins, cells, tissues and related materials derived from human sources that are used *in vitro* or *ex vivo* to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance

	is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways. All such reports should be placed in this section. Studies using biomaterials to address other properties (e.g., sterility or Pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Module 4).
5.3.3	**Reports of Human Pharmacokinetic (PK) Studies**
5.3.3.1	*PK and Initial Tolerability Study Reports* Reports of PK and initial tolerability studies in healthy subjects should be placed in this section. These PK studies are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or faeces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells. On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in this section. These studies should characterize the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g.,

	due to enzyme induction or formation of antibodies) are of particular interest and should be included in this section.
5.3.3.2	*Intrinsic Factor and Extrinsic Factor PK Study Reports* Reports of PK studies examining the influence of intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors should be placed in this section.
5.3.3.3	*Population PK Study Reports* Reports of population PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials, should be placed in this section.
5.3.4	**Reports of Human Pharmacodynamic (PD) Studies** Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in Section 5.3.5. This section should include reports of ▪ Studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers) ▪ Short-term studies of the main clinical effect, and ▪ PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and

	metabolite concentrations is usually of interest, PD information is frequently collected in dose response studies or together with drug concentration information in PK studies (concentration-response or PK/PD studies). Dose-finding, PD and/or PK-PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD and/or PK/PD studies conducted in healthy subjects and/or in patients should be placed in this section. In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in Section 5.3.5, not in Section 5.3.4.
5.3.5	**Reports of Efficacy and Safety Studies** This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all ongoing studies of the drug in proposed and non-proposed indications. The study reports should

	provide the level of detail appropriate to the study and its role in the application. Within Section 5.3.5, studies should be organised by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated, with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section. In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Section 5.3.5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate Section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Section 5.3.5 and referenced as necessary in other Sections 5.3.5, e.g., Section 5.3.5A, Section 5.3.5B.
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* Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included here. This also includes studies in conditions that are not the subject of the marketing application.

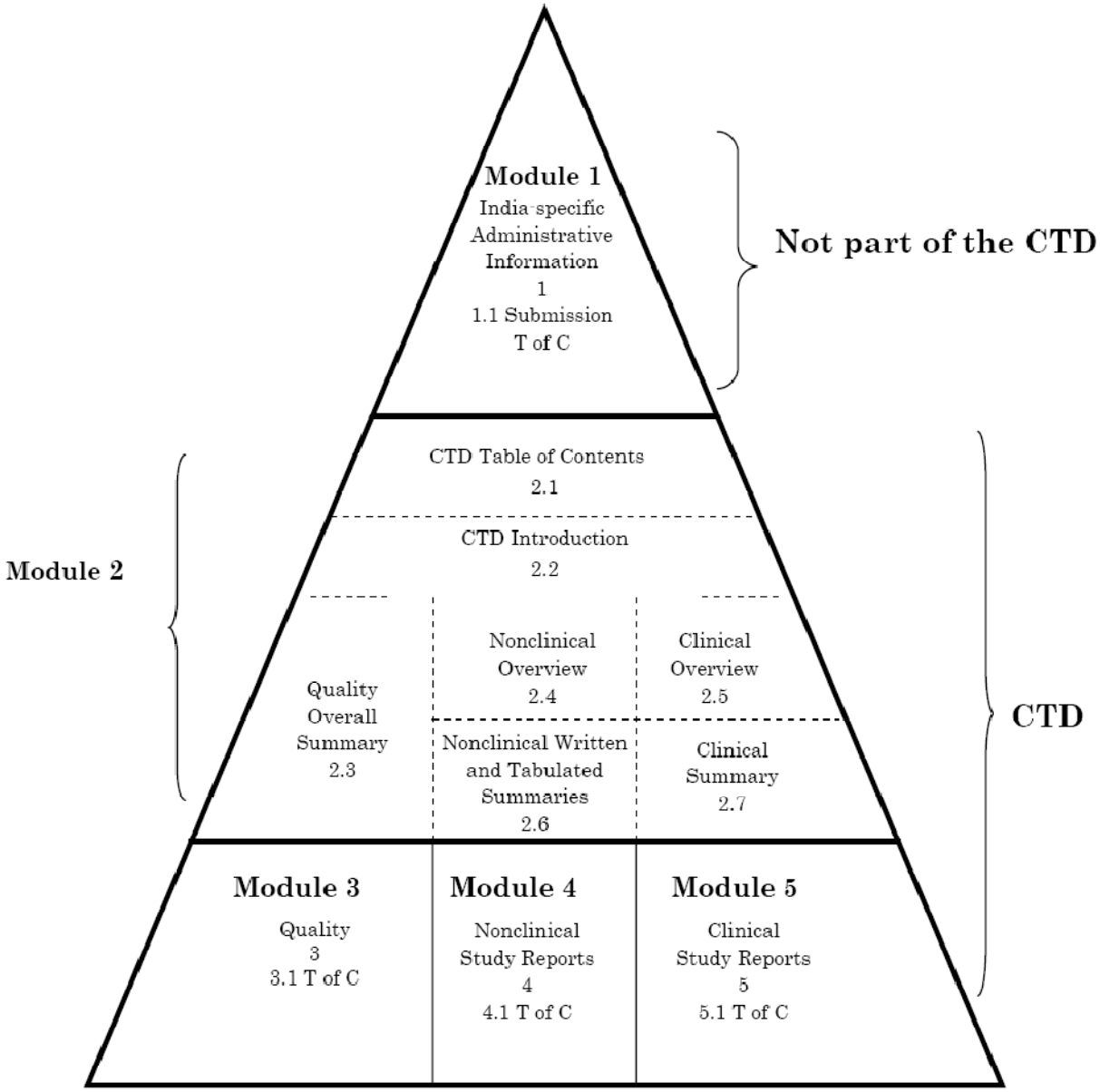
5.3.5.3	*Reports of Analyses of Data from More than One Study* Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in this section.
5.3.5.4	*Other Study Reports* This section can include: ▪ Reports of interim analyses of studies pertinent to the claimed indications ▪ Reports of controlled safety studies not reported elsewhere ▪ Reports of controlled or uncontrolled studies not related to the claimed indication ▪ Published reports of clinical experiences with the medicinal product not included in *Section 5.3.5.1*. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in *Section 5.3.5.1* ▪ Reports of ongoing studies
5.3.6	**Reports of Post-Marketing Experience**

	For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included.
5.3.7	**Case Report Forms and Individual Patient Listings** Case report forms and individual patient data listings from the clinical study reports, should be placed in this section, in the same order as the clinical study reports and indexed by study.
5.4	**LITERATURE REFERENCES** Copies of referenced documents, including important published articles, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.
LIST OF ABBREVIATIONS	

7 ANNEXURES

7.1 ANNEXURE I: DIAGRAMMATIC REPRESENTATION OF CTD

Diagrammatic Representation of Organization of CTD



7.2 ANNEXURE II: FORMAT FOR UNDERTAKING OR DECLARATION

I *<Name>*, authorized representative of *<Name of the Company>* having its registered office at *<Address >* herein after referred to as "The Company", do hereby solemnly affirm and state as under: *(Please delete the sections that are not applicable)*

1. The company shall comply with all the conditions imposed on the licensing and/or Market Authorization of the applied drugs as per the provisions of the Drugs and Cosmetics Act and Rules made there under.
2. The company declare that the company is manufacturing the drugs at the premises specified in Module I of the submitted documents, and the company shall from time to time report any change of premises on which manufacture will be carried on and in cases where manufacture is carried on in more than one factory any change in the distribution of functions between the factories.
3. The company shall comply with the provisions of Part IX of the Drugs and Cosmetics Rules, 1945.
4. Every drug manufactured by us for licensing and / market authorization shall be as regard strength, quality and purity conforms with the provisions of Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules 1945, and their amendments from time to time.
5. The company shall from time to time report for any change or manufacturing process, or in packaging, or in labeling, or in testing, or in documentation of any of the drugs, pertaining to the

product permission, licence and/or market authorization to be granted to us. Where any change in respect of any of the drugs has taken place, in respect of any of the above matters, we shall inform the same to the licensing authority in writing within 30 days from the date of such changes. In such cases, where there will be any major change/modification in manufacturing or in processing or in testing, or in documentation, as the case may be, at the discretion of the licensing authority, we shall obtain necessary approval by submitting a separate application, along with the applicable fee under Drugs and Cosmetics Rules 1945.

6. The company shall from time to time report for any administrative action taken due to adverse reaction, viz. market withdrawal, regulatory restriction, or cancellation of authorization of any drug pertaining licensing and/or Market Authorization declared by any Regulatory Authority of any country where the drug is marketed/sold or distributed. In such cases, the CDSCO may direct appropriate course of action including the withdrawal of the drug from Indian market.
7. The company shall comply with such further requirements, if any, as may be specified, by the Government of India, under the Act and the rules made there under.
8. The company shall allow the licensing authority and/or any person authorized by him in that behalf to enter and inspect the manufacturing premises and to examine the process/procedure and documents in respect of any drug manufactured by us for which the new drug application has been made.
9. The company shall allow the licensing authority or any person authorized by him in that behalf to take samples of the drugs

concerned for test, analysis or examination, if considered necessary by the licensing authority.

10. The company hereby declares that the submitted information/documents are factual and relevant to the application for new drug approval.

Place:

Date:

Signature of the manufacturer

[*or his authorized agent*]

Seal / Stamp

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION CDSCO CDSCO MINISTRY OF HEALTH, GOVERNMENT OF INDIA

7.3 ANNEXURE III: FORMAT FOR LISTING OF CLINICAL STUDIES

(This is the preferred format, illustrated with example)

Type of Study	Study Identifier	Location of Study Report	Objective (s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen & Route	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	001	Vol 3, Sec. 1.1, p. 183	Absolute BA IV vs Tablet	Cross-over	Tablet, 50mg single dose, oral, 10 mg IV	20	Healthy Subjects	Single dose	Complete; Abbreviated
BE	002	Vol 4, Sec. 1.2, p. 254	Compare clinical study and to-be-marketed formulation	Cross-over	Two tablet formulations, 50 mg, oral	32	Healthy Subjects	Single dose	Complete; Abbreviated
PK	1010	Vol 6, Sec. 3.3, p. 29	Define PK	Cross-over	Tablet, 50mg single dose, oral	50	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	Randomised placebo-controlled	Tablet, 50mg, multiple dose, oral, every 8 hrs	24 (12 drug, 12 placebo)	Patients with primary hypertension	2 weeks	Ongoing; Interim
Efficacy	035	Vol 10, Sec. 5.1, p. 1286	Long term; Efficacy & Safety; Population PK analysis	Randomised active-controlled	Tablet, 50mg, oral, every 8 hrs	300 (152 test drug, 148 active control)	Patients with primary hypertension	48 weeks	Complete; Full