الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guidance for Submission

Version 2

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الهيئة العامة للغذاء والدواء
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Drug Sector

Saudi Food & Drug Authority

Kingdome of Saudi Arabia

Please visit SFDA's website at http://www.sfda.gov.sa/En/Drug for the latest update

Drug Sector

Vision & Mission

Vision

To be the leading regional Drug Regulatory Authority for pharmaceuticals and safety of cosmetic products, with professional excellence and services that contribute to the protection and advancement of public health in the Kingdom of Saudi Arabia.

الرؤية

أن يكون قطاع الدواء رائداً إقليميا في الرقابة على الأدوية وسلامة مستحضرات التجميل، ويقدم خدماته بمهنية متميزة تسهم في حماية وتعزيز الصحة في المملكة العربية السعودية.

Mission

Protecting public health by ensuring safety, quality, efficacy and accessibility of human, veterinary drugs and biological products, and safety of cosmetics, through administration of a national regulatory system which is consistent with international best practice. Through our mission, we also provide accurate and scientific-based information to the public and healthcare professionals.

الرسالة

حماية الصحة العامة من خلال ضمان أمان وجودة وفعالية وتوفر الأدوية البشرية والبيطرية والمنتجات الحيوية وسلامة مواد التجميل عبر تطبيق نظام وطني للرقابة متوافق مع أفضل الممارسات الدولية وتقديم المعلومات الدوائية المبنية على أسس علمية للعامة والمهنيين الصحيين.

Document Control

Version	Date	Author(s)	Comments
1.0	11/05/2009	Licensing department	Initial draft for internal consultation
1.1	20/05/2009	Licensing department	Draft revision
1.2	06/06/2009	Licensing department	Draft revision
1.3	28/06/2009	Licensing department	Revisions after management discussion
2.0	08/07/2009	Licensing department	Published for comments

Table of Contents

1 Introduction

The Drug Sector in the Saudi Food & Drug Authority (SFDA) has developed this document, "Guidance for Submission" to assist applicants and industry in the preparation and submission of drug applications for new Marketing Authorization (MA) as well as renewals and variations to existing products to the SFDA. The guidance provides an outline of the way the Framework will be managed with respect to drug applications by the SFDA.

It is intended to provide clarification to applicants of the way in which the Drug Sector in the SFDA manage information and material submitted in accordance with the *Regulatory framework for Drug Approvals (version 4).* Also, it provides assistance to comply with the requirements of filing and maintenance of their application.

Industry representatives, as well as the staff of the SFDA responsible for the drug application management, will follow this guidance and operational directions in various areas, including the handling of application information, procedure related to drug assessment, clarification and performance target of drug assessments.

To maintain its consistency and enhanced transparency, this guidance will be updated regularly to reflect the current practices in regulatory sciences. It is expected that this guidance and any amendments to it will create efficiency in the drug application management and reduce the number of clarification requests.

It should be noted that the SFDA has the right to request any information and data within the context of this guidance in order to assess adequately the safety, efficacy and quality of any medicinal products available in the Kingdom of Saudi Arabia. The SFDA is committed to ensuring that such requests are justifiable and decisions are clearly documented.

2 Scope

This guidance document applies to all **drug submission types**:

- Generics
- New drugs (NCE and Known Active Substances)
- Biologics
- Radiopharmaceuticals
- Herbal & Health products
- Veterinary products
- Renewal of MA
- Variations type I & II

All submitted information and material will be screened to ensure that it is complete and of suitable quality to be reviewed. The same management principles will be applied consistently to all submission types.

This guidance document covers the preparation and filling requirements for submissions in paper-based CTD and electronic format. It is based on the ICH CTD and the eCTD Specifications, and the SFDA Regulatory Framework for Drug Approval.

This guidance document DOES NOT currently apply to **Clinical Trials Application**.

3 Registration Process

All Applications will be subjected to the following procedures:

1. Online Filing of Application

The applicant shall fill up the appropriate application form in the SFDA website. Once completed, application form cannot be submitted unless the payment details are entered into the system. A reference number will be assigned to the application once submitted to facilitate the communication with the SFDA. Then, the applicant will be given an opportunity to book an appointment to hand over the drug application (figure 1). The earliest appointment is 1 week, up to 12 weeks in advance. An automatic reminder will be sent 3 days before the appointment. The applicant can reschedule a week before the chosen appointment. If it is missed, the earliest appointment that can be booked is one month after the missed one.

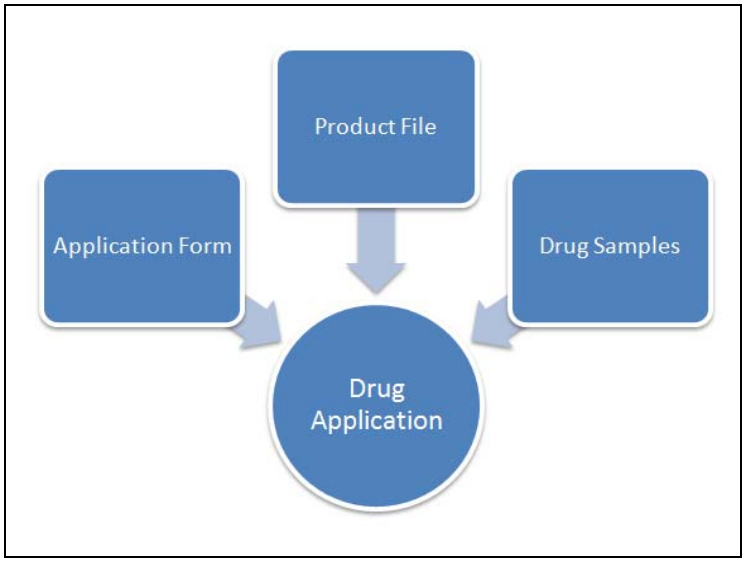

Figure 1: A "Drug Application" includes the application form, the product file and the drug samples.

2. Acceptance of Drug Application

Upon receipt of the drug application in the appointment day, a checklist for 'Phase I Validation' will be used to verify that the information and materials provided are complete.

a. **Drug application Without Deficiencies**:

The applicant will be notified of the acceptability by printing an Acknowledgement Letter. Then, the drug application will be forwarded to the product manager (Licensing Department) for further processing and assessment. Once these applications are accepted, they will be assessed in the order in which they are received.

b. **Drug application With Deficiencies**:

If deficiencies are identified, an Acknowledgment Letter stating the deficiencies will be issued. The applicant will be required to submit the requested information within 60 days from the date of the letter. The applicant will be given only ONE opportunity to complete the file.

- If the applicant has provided the requested information within 60 days, the application will be accepted and the applicant will be notified of the acceptability by e-mail. The drug application will be forwarded to the product manager for further processing and assessment.
- If the applicant has provided the requested information within 60 days but it was found to be still incomplete, the application will be rejected and the applicant will be required to file a new application. An acknowledgment letter will be provided to the applicant.
- If the applicant fails to provide the requested information within 60 days, the drug application will be rejected and securely disposed of.

3. Phase II Validation

After accepting the drug application from the applicant, the submitted information and material will be validated to ensure that it has suitable quality to be assessed. However, if deficiencies are identified, the applicant will be asked to submit the required information, and it will follow one of the following cases:

- If the applicant has provided the requested information within 60 days, the product file will be forwarded for further processing and assessment. The applicant will be notified by e-mail.
- If the applicant has provided the requested information within 60 days but it was found to be still incomplete, SFDA will study the case and may extend the period for another maximum 30 days. The applicant will be notified by e-mail.
- If the applicant fails to provide the requested information within 60 days, the drug application will be rejected and securely disposed of.

4. Assessment of Application

All applications will be assessed in terms of quality, safety and efficacy – as needed – depending on the type of the product.

If issues are identified during the assessment, these issues will be resolved through electronic Inquiry Forms. Although there is no limitation of inquiries, it is expected that these issues be resolved by two to three inquiries. Responses to inquiries are required within 30 days.

5. Pricing

The pricing will be calculated according to the pricing rules outlined in the pricing guideline.

6. Testing

All drug products will be subjected to appropriate testing according to the type of the application and dosage form, to ensure the quality of the products as required by Drug Law. Moreover, the applicant is requested to deliver the samples to SFDA headquarters as part of the drug application. There will be no direct contact between the applicant and SFDAs laboratory.

7. Inspection

The head of the inspection unit will communicate with the applicant to decide the appropriate time for inspection – if needed, depending on the schedules of the inspectors. After the inspection is done, an inspection report will be written and a copy of this report will be sent to the applicant. In case of deficiencies, further details will follow.

8. Stop-clock

The stop-clock starts whenever SFDA issues an Inquiry Form. Inquiries may be raised at any time from the Phase II Validation to SFDA decision. The stop-clock ends whenever SFDA receives complete and acceptable responses from the applicant.

If the applicant faces difficulties in responding to inquiries within the specified time, applicant should contact SFDA as soon as possible. A drug application will be considered rejected if the stop-clock time exceeds the SFDA deadline.

9. SFDA Decision

The final decision is made based on the outcome of SFDA's assessment, pricing, testing and inspection. The decision can be one of the following:

- **Approval**: when the drug application has satisfied the registration requirements for quality, safety and efficacy.
- **More information is needed**: when the drug application has minor deficiencies.
- **Rejection**: when the drug application has not satisfied the registration requirements.

10. Appeal Process

The applicant will have the right to appeal within 30 days against the SFDA decision. The relevant guidance will be published soon.

4 Structure and Content of Submission

4.1 Structure of Submission:

The SFDA will require all applicants to submit their applications in accordance to the ICH Common Technical Document (CTD) format. For more information on the CTD, please refer to appendix D.

The dossier requirements for each application will differ, depending on the type of application. The table below outlines the CTD Modules required for all types of applications:

	CTD Modules				
Type of drug submission	**1**	**2**	**3**	**4**	**5**
Generics	**R**[1]	**P**[2]	**R**	**P**	**P**
New drugs	**R**	**R**	**R**	**R**	**R**
Biologics	**R**	**R**	**R**	**R**	**R**
Radiopharmaceutical	**R**	**R**	**R**	**R**	**R**
Herbal & Health product	**R**	**P**	**R**	**P**	**P**

4.2 Content of Submission

The content will differ from a drug type to another. For more details, see appendix A.

It is important to remember that the CTD provides a format for an MAA and does not indicate the content of a dossier and which studies should be performed. Regional and national requirements may affect the content of the dossier; therefore the dossier will not necessarily be identical for all regions.

[1] **R**: Required
[2] **P**: Partially required

Relevant guidelines, such as Stability guideline, should be followed in providing the information or studies. For updated guidelines, visit the SFDA website.

4.3 Module 1: Regional Administrative Information

This module includes the regional required information specific to SFDA, such as administrative information and certificates. The information to be provided are identified below and includes:

- 1.0 Cover letter:

  The applicant shall include a cover letter for each drug type submission. A template is provided in appendix J.

- 1.1 Comprehensive table of contents (ToC):

  The ToC for the entire submission should list all documents included in Module 1 and the contents of Modules 2 to 5 to the level of detail or 'granularity' defined in the Organization of the Common Technical Document guidance.

- 1.2 Application Form:

  The completed and **signed** Application Form should be presented in this section.

- 1.3 Product Information:

  This section contains the Summary of Product Characteristics (SPC), Labeling, Patient information leaflet (PIL) in Arabic and English, Artwork and the samples. SPC, Labeling and PIL information shall follow the WHO templates.

- 1.4 Information on the Experts:

  The relevant quality, non-clinical and clinical expert declaration(s), signature(s) and CV(s) must be provided – if applicable, corresponding to the Overview/Summary submitted in Module 2.3, 2.4 and 2.5 respectively.

- 1.5 Environmental Risk Assessment:

  The application for MA shall be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment. Such risk may include those arising from use, storage disposal and synthesis or manufacture of medicinal products.

- 1.6 Pharmacovigilance:

  It shall contain a detailed description of the pharmacovigilance system including the proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction.

- 1.7 Certificates:

  This section contains different type of required certificates such as Certificate of Pharmaceutical Product (CPP), certificate of analysis and others.

- 1.8 Pricing:

  It should contain the price of the product in countries listed in appendix I.

- 1.9 Responses to questions:

  The applicant answers on the SFDA questions shall be placed here. This part is only applicable to eCTD submissions.

5 Presentation of the Product File

BOTH the hard-copy (paper-based) and soft-copy (electronic-based) of the product file shall be submitted by applicants. The hard-copy shall be in the CTD structure. Whereas, the soft-copy shall be either as:

a. eCTD (appendix D), or

b. An electronic version of the paper-based submission in a specific structure (appendix B).

5.1 Hardcopy and Softcopy Requirements:

For the **hardcopy** (paper-submission), the full dossier should be bound into one volume (ring binder) or more according to the number of pages. For every 300 pages, one volume is needed.

The ring binder specifications:

- A4 D-ring 2-ring binder (box file)
- Binder Dimensions: width 26.5cm, height 34cm and thickness 7.5cm (26.5 X 34 cm X 7.5 cm)
- Label: should contain the following information (figure 2):
    1. Reference number (generated from the system)
    2. Company name
    3. Product trade name
    4. Product Generic name
    5. Date of submission (DD/MM/YYYY)
    6. Number of volumes
    7. Type of submission (e.g. new, renew or variation)
- If more than one volume is needed, avoid spanning the content of a Part or a Module of the dossier over two volumes - if applicable.
- Tabs should be used to separate the modules

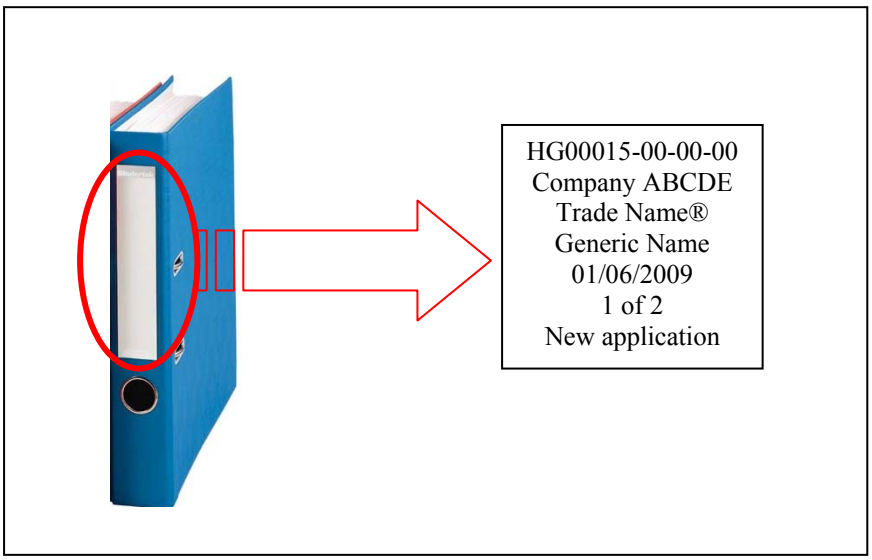

Figure 2: the binder label information

For the **softcopy** (electronic-submission), each CD or DVD submitted should include the following label information, clearly presented and printed on the media:

- The label should be printed on the CD with the font of 12 Times New Roman
- The reference number
- The company name
- The product trade name
- The Generic name
- Date of submission (DD/MM/YYYY)
- Number of media units per full set and an indication of the place of the individual CD/DVD within this set (e.g. 1(4), 2(4)...)
- The submission type of each submission(s) contained on the CD/DVD (e.g. Initial Application, Variation Type II)
- The sequence number(s) of the eCTD submissions contained on the CD/DVD (when applicable)

5.2 Number of copies:

Applicants should submit TWO softcopies (identical) and ONE hardcopy of the product file for all drug submission types. However, in case of **NCE,**

biologicals and biosimilars only module 1, 2 & 3 are required as a hardcopy (i.e. the softcopy will contain all the CTD structure).

5.3 MEDIA

The electronic submission may only be submitted in CD or DVD (single or dual layer). The disc must not be bootable or have auto-start programs. Two electronic copies are required to be submitted.

Applicant must provide the electronic information on the smallest number of media units possible, taking into consideration the size of the submission. Currently both CD-ROM and DVD ISO 9660 are considered an acceptable media standard.

If more than one CD-ROM or DVD is needed, avoid spanning the content of a Part or a Module of the dossier over two CD-ROMs or DVDs.

Hard media (e.g. CD, DVD) must be used for the submission of all CTD documents and eCTDs. It is appreciated that it may be necessary at certain times in the evaluation process, to submit certain documents via email in the first instance in order to ensure that the documents are received by SFDA in a timely manner. However, it is expected to receive an exact copy of the same submission on hard media as soon as possible, and this electronic submission will become the formal SFDA record. The electronic submission will be appropriately processed once received on hard media. The SFDA strongly advises that eCTD sequences should ONLY be submitted via CD or DVD as far as possible to ensure that only one communication channel is used.

However**,** the SFDA will not accept any hardware (laptops, desktops, thumb drives, hard drive, floppy discs etc.) from applicants in connection with the electronic submission.

5.3.1 System compatibility:

The electronic submission (as provided) must be directly readable and usable on SFDA hardware and software.

Although it is the policy of the SFDA to maintain desktop configurations and IT infrastructure in line with common office standards,

the electronic information provided in the submission must not only be readable on the latest operating system, but support a reasonable number of backward versions of windows operating systems.

5.4 Security

There are various aspects related to security. The physical security of the submission during transportation/transmission is the responsibility of the applicant. Once received within the SFDA, security and submission integrity is the sole responsibility of the SFDA. In this respect, it should be noted that the SFDA will take appropriate measures to prevent loss, unauthorized duplication and/or access or theft of regulatory information presented both on paper and electronic media that are distributed throughout the SFDA.

5.4.1 Password protection:

One-time security settings or password protection of electronic submissions for security purposes is *not* acceptable during transportation/transmission from the applicant to the SFDA.

Applicants should also *not* include any file level security settings or password protection for individual files in the electronic submission.

Applicants should allow printing, annotations to the documents, and selection of text and graphics. The Internal security and access control processes in the SFDA maintain the integrity of the submitted files.

5.4.2 Virus protection:

The applicant is responsible for checking the submission for viruses. Checking must be performed with an up-to-date and well-recognized virus-checker.

After receipt of the submission at the SFDA, a similar internal virus check will be performed. If a virus is detected it can constitute grounds for refusal of the electronic submission.

6 Document Requirements

6.1 Legibility and Size

All documents should be legible. The page size, including tables, shall be uniform.

6.2 Pagination

The pagination may be sequential for the entire submission or by volume. Cross-references should include both volume and page number.

6.3 Language

Information and documents supporting a drug application – such as certificates and approval letters– must be either in Arabic or English. If documents are neither in Arabic nor English, a translation to English from an authorized translation office and authentication from the Saudi Embassy in the COO are required.

6.4 Authentication

Authentication – also known as legalization – refers to the process whereby the origins of a document are attested. Authentication of documents are made to SFDA by the Health authority and/or the Ministry of Foreign affairs in the country of origin, in addition to the Saudi Arabia Embassy or Consulate where the document was issued.

Certificates that must be authenticated are:

1. CPP or Free Sale Certificate
2. Certificate of analysis
3. Pork-free declaration
4. Price List

Appendices

Appendix A: Data Requirements

The data requirements for each application will differ, depending on the drug submission type. However, all the required data should be in accordance with the CTD structure.

- In case of **New Chemical Entity (NCE), Biologicals and Biosimilars** ALL the CTD Modules are required.
- On the other hand the table below outlines the CTD Modules required for **Generics (Human and Veterinary) Herbal & Health products**[3]:

G: Generics **R: Required**
H: Herbal & Health products **O: Optional**[4]

Section	Requirements	G	H
Module 1	**Regional Administrative Information**		
1.0	Cover letter	R	R
1.1	Comprehensive Table of content	R	R
1.2	Application Form	R	R
1.3	Product Information		
1.3.1	Summary of Product Characteristics (SPC)	R	R
1.3.2	Labeling	R	R
1.3.3	Patient information leaflet (PIL)		
1.3.3.1	Arabic leaflet	R	R
1.3.3.2	English leaflet	R	R
1.3.4	Artwork (Mock-ups)	R	R
1.3.5	Samples	R	R
1.4	Information on the experts		
1.4.1	Quality	O	O
1.4.2	Non-Clinical	O	O
1.4.3	Clinical	O	O
1.5	Environmental Risk Assessment		
1.5.1	Non-Genetically Modified Organism (Non-GMO)	O	O
1.5.2	GMO	O	O
1.6	Pharmacovigilance		
1.6.1	Pharmacovigilance System	R	R
1.6.2	Risk Management Plan	O	
1.7	Certificates		
1.7.1	CPP or Free-sales	R	R
1.7.2	Certificate of analysis – Drug Substance	R	R
1.7.3	Certificate of analysis – Excipients	O	O
1.7.4	Alcohol-free declaration	R	R
1.7.5	Pork-free declaration	R	R

[3] Blank fields are not required at this stage or not applicable for that specific drug submission type.
[4] Optional means that it might not be needed at this stage

Section	Requirements	G	H
1.7.6	The diluents and coloring agents in the product formula	R	R
1.7.7	Patent Information	R	R
1.8	Pricing		
1.8.1	Price list	R	R
1.8.2	Other documents related	O	O
1.9	Responses to questions	R	R
Module 2[5]	**Common Technical Document Summaries**		
2.1	Table of Contents of Module 2-5		
2.2	Introduction		
2.3	Quality Overall Summary		
	Introduction		
2.3.S	Drug substance		
2.3.S.1	General Information		
2.3.S.2	Manufacture		
2.3.S.3	Characterization		
2.3.S.4	Control of Drug Substance		
2.3.S.5	Reference Standards or Materials		
2.3.S.6	Container/Closure System		
2.3.S.7	Stability		
2.3.P	Drug Product		
2.3.P.1	Description and Composition of the Drug Product		
2.3.P.2	Pharmaceutical Development		
2.3.P.3	Manufacture		
2.3.P.4	Control of Excipients		
2.3.P.5	Control of Drug Product		
2.3.P.6	Reference Standards or Materials		
2.3.P.7	Container/Closure System		
2.3.P.8	Stability		
2.3.A	Appendices		
2.3.A.1	Facilities and Equipment		
2.3.A.2	Adventitious Agents Safety Evaluation		
2.3.A.3	Novel Excipients		
2.3.R	Regional Information		
2.4	Nonclinical Overview		
2.5	Overview of the Nonclinical Testing Strategy		
2.5.1	Product Development Rationale		
2.5.2	Overview of Biopharmaceutics		
2.5.3	Overview of Clinical Pharmacology		
2.5.4	Overview of Efficacy		
2.5.5	Overview of Safety		
2.5.6	Benefits and Risks Conclusions		

[5] Module 2 Should reflect the information provided in modules 3, 4 and 5.

Section	Requirements	G	H
2.5.7	References		
2.6	Non clinical written and tabulated summaries: Pharmacology, pharmacokinetics Toxicology		
2.6.1	Introduction		
2.6.2	Pharmacology Written Summary		
2.6.2.1	Brief Summary		
2.6.2.2	Primary Pharmacodynamics		
2.6.2.3	Secondary Pharmacodynamics		
2.6.2.4	Safety Pharmacology		
2.6.2.5	Pharmacodynamic Drug Interactions		
2.6.2.6	Discussion and Conclusions		
2.6.2.7	Tables and Figures		
2.6.3	Pharmacology Tabulated Summary		
2.6.4	Pharmacokinetics Written Summary		
2.6.4.1	Brief Summary		
2.6.4.2	Methods of Analysis		
2.6.4.3	Absorption		
2.6.4.4	Distribution		
2.6.4.5	Metabolism (interspecies comparison)		
2.6.4.6	Excretion		
2.6.4.7	Pharmacokinetic Drug Interactions		
2.6.4.8	Other Pharmacokinetic Studies		
2.6.4.9	Discussion and Conclusions		
2.6.4.10	Tables and Figures		
2.6.5	Pharmacokinetics Tabulated Summary		
2.6.6	Toxicology Written Summary		
2.6.6.1	Brief Summary		
2.6.6.2	Single-Dose Toxicity		
2.6.6.3	Repeat-Dose Toxicity		
2.6.6.4	Genotoxicity		
2.6.6.5	Carcinogenicity		
2.6.6.6	Reproductive and Developmental Toxicity		
2.6.6.7	Local Tolerance		
2.6.6.8	Other Toxicity Studies (if available)		
2.6.6.9	Discussion and Conclusions		
2.6.6.10	References		
2.6.7	Toxicology Tabulated Summary		
2.7	Clinical Summary		
2.7.1	Summary of Biopharmaceutic and Associated Analytical Methods		
2.7.1.1	Background and Overview		
2.7.1.2	Summary of Results of Individual Studies		
2.7.1.3	Comparison and Analyses of Results Across Studies		
2.7.1.4	Appendix		

Section	Requirements	G	H
2.7.2	Summary of Clinical Pharmacology Studies		
2.7.2.1	Background and Overview		
2.7.2.2	Summary of Results of Individual Studies		
2.7.2.3	Comparison and Analyses of Results Across Studies		
2.7.2.4	Special Studies		
2.7.2.5	Appendix		
2.7.3	Summary of Clinical Efficacy		
2.7.3.1	Background and Overview of Clinical Efficacy		
2.7.3.2	Summary of Results of Individual Studies		
2.7.3.3	Comparison and Analyses of Results Across Studies		
2.7.3.3.1	Study Populations		
2.7.3.3.2	Comparison of Efficacy Results Across All Studies		
2.7.3.3.3	Comparison of Results in Sub-Populations		
2.7.3.4	Analysis of Clinical Information Relevant to Dosing Recommendations		
2.7.3.5	Persistence of Efficacy and/or Tolerance Effects		
2.7.3.6	Appendix		
2.7.4	Summary of Clinical Safety		
2.7.4.1	Exposure to the Drug		
2.7.4.1.1	Overall Safety Evaluation Plan and Narratives of Safety Studies		
2.7.4.1.2	Overall Extent of Exposure		
2.7.4.1.3	Demographic and Other Characteristics of Study Population		
2.7.4.2	Adverse Events		
2.7.4.2.1	Analysis of Adverse Events by Organ System or Syndrome		
2.7.4.2.2	Narratives		
2.7.4.3	Clinical Laboratory Evaluations		
2.7.4.4	Vital Signs, Physical Findings, Observations Related to Safety		
2.7.4.5	Safety in Special Groups and Situations		
2.7.4.5.1	Intrinsic Factors		
2.7.4.5.2	Extrinsic Factors		
2.7.4.5.3	Drug Interactions		
2.7.4.5.4	Use in Pregnancy and Lactation		
2.7.4.5.5	Overdose		
2.7.4.5.6	Drug Abuse		
2.7.4.5.7	Withdrawal and Rebound		
2.7.4.5.8	Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability		
2.7.4.6	Post-Marketing Data		
2.7.4.7	Appendix		
2.7.5	References		
2.7.6	Synopses of Individual Studies		
Module 3	**Quality**		

Section	Requirements	G	H
3.1	Table of Contents of Module 3	R	R
3.2	Body of data		
3.2.S	Drug Substance		
3.2.S.1	General Information		
3.2.S.1.1	Nomenclature	R	R
3.2.S.1.2	Structure	R	R
3.2.S.1.3	General Properties	R	R
3.2.S.2	Manufacture		
3.2.S.2.1	Manufacturer(s)	R	R
3.2.S.2.2	Description of Process and Process Controls	R	O
3.2.S.2.3	Control of Materials	R	O
3.2.S.2.4	Control of Critical Steps and Intermediates	R	O
3.2.S.2.5	Process Validation and/or Evaluation	R	O
3.2.S.2.6	Manufacturing Process Development	R	O
3.2.S.3	Characterization		
3.2.S.3.1	Elucidation of Structure and Other Characteristics	R	O
3.2.S.3.2	Impurities	R	R
3.2.S.4	Control of Drug Substance		
3.2.S.4.1	Specifications	R	O
3.2.S.4.2	Analytical Procedures	R	O
3.2.S.4.3	Validation of Analytical Procedures	R	O
3.2.S.4.4	Batch Analyses	R	R
3.2.S.4.5	Justification of Specification	R	O
3.2.S.5	Reference Standards or Materials	R	O
3.2.S.6	Container/Closure Systems	R	O
3.2.S.7	Stability		
3.2.S.7.1	Stability Summary and Conclusions	R	O
3.2.S.7.2	Post-approval Stability Protocol and Commitment	R	O
3.2.S.7.3	Stability Data	R	O
3.2.P	Drug Product		
3.2.P.1	Description and Composition of the Drug Product	R	R
3.2.P.2	Pharmaceutical Development		
3.2.P.2.1	Components of the Drug Product		
3.2.P.2.1.1	Drug substance	R	R
3.2.P.2.1.2	Excipients	R	R
3.2.P.2.2	Drug Product		
3.2.P.2.2.1	Formulation Development	O	O
3.2.P.2.2.2	Overages	R	R
3.2.P.2.2.3	Physiochemical and Biological Properties	R	R
3.2.P.2.3	Manufacturing Process Development	R	R
3.2.P.2.4	Container Closure System	R	R
3.2.P.2.5	Microbiological Attributes	R	R
3.2.P.2.6	Compatibility	O	O

Section	Requirements	G	H
3.2.P.3	Manufacture		
3.2.P.3.1	Manufacturer(s)	R	R
3.2.P.3.2	Batch Formula	R	R
3.2.P.3.3	Description of Manufacturing Process and Process Controls	R	R
3.2.P.3.4	Controls of Critical Steps and Intermediates	R	O
3.2.P.3.5	Process Validation and/or Evaluation	R	O
3.2.P.4	Control of Excipients		
3.2.P.4.1	Specifications	R	R
3.2.P.4.2	Analytical Procedures	R	R
3.2.P.4.3	Validation of Analytical Procedures	R	R
3.2.P.4.4	Justification of Specifications	R	R
3.2.P.4.5	Excipients of Human or Animal Origin	R	R
3.2.P.4.6	Novel Excipients	R	R
3.2.P.5	Control of Drug Product		
3.2.P.5.1	Specifications	R	R
3.2.P.5.2	Analytical Procedures	R	R
3.2.P.5.3	Validation of Analytical Procedures	R	R
3.2.P.5.4	Batch Analyses	R	R
3.2.P.5.5	Characterization of Impurities	R	R
3.2.P.5.6	Justification of Specifications	R	R
3.2.P.6	Reference Standards or Materials	R	R
3.2.P.7	Container/Closure System	R	R
3.2.P.8	Stability		
3.2.P.8.1	Stability Summary and Conclusions	R	R
3.2.P.8.2	Post-Approval Stability Protocol and Stability Commitments	R	R
3.2.P.8.3	Stability Data	R	R
3.2.A	Appendices		
3.2.A.1	Facilities and Equipment	O	O
3.2.A.2	Adventitious Agents Safety Evaluation	O	O
3.2.A.3	Excipients	R	R
3.2.R	Regional Information		
3.2.R.1	Alcohol Content Declaration	R	R
3.2.R.2	Porcine/Pork – content/origin	R	R
3.2.R.3	The diluents and coloring agents in the product formula		
3.3	Literature References	R	R
Module 4	**Non-Clinical Study Reports**		
4.1	Table of Contents of Module 4		R
4.2	Study Reports		
4.2.1	Pharmacology		
4.2.1.1	Primary Pharmacodynamics		R
4.2.1.2	Secondary Pharmacodynamics		R

Section	Requirements	G	H
4.2.1.3	Safety Pharmacology		R
4.2.1.4	Pharmacodynamic Drug Interactions		R
4.2.2	Pharmacokinetics		
4.2.2.1	Analytical Methods and Validation Reports		R
4.2.2.2	Absorption		R
4.2.2.3	Distribution		R
4.2.2.4	Metabolism		R
4.2.2.5	Excretion		R
4.2.2.6	Pharmacokinetic Drug Interactions		R
4.2.2.7	Other Pharmacokinetic Studies		R
4.2.3	Toxicology		R
4.2.3.1	Single-Dose Toxicity		R
4.2.3.2	Repeat-Dose Toxicity		R
4.2.3.3	Genotoxicity		
4.2.3.3.1	In vitro Studies		
4.2.3.3.2	In vivo Studies		
4.2.3.4	Carcinogenicity		
4.2.3.4.1	Long Term Studies		
4.2.3.4.2	Short or medium term studies		
4.2.3.4.3	Other studies		
4.2.3.5	Reproductive and Development Toxicity		
4.2.3.5.1	Fertility and Embryonic Development		
4.2.3.5.2	Embryo-Fetal Development		
4.2.3.5.3	Pre- and Post-natal Development & Maternal Function		
4.2.3.5.4	Offspring, Juvenile, Second & Third-Generation Studies		
4.2.3.6	Local Tolerance		
4.2.3.7	Other Toxicity Studies		
4.2.3.7.1	Antigenicity		
4.2.3.7.2	Immunogenicity		
4.2.3.7.3	Mechanistic Studies (not included elsewhere)		
4.2.3.7.4	Dependence		
4.2.3.7.5	Metabolites		
4.2.3.7.6	Impurities		
4.2.3.7.7	Other		
4.3	Literature References	O	O
Module 5	**Clinical Study Reports**		
5.1	Table of Contents of Module 5	R	R
5.2	Tabular Listing of All Clinical Studies	R	R
5.3	Clinical Study Reports		
5.3.1	Reports of Biopharmaceutic Studies		
5.3.1.1	Bioavailability (BA) Study Reports	R	O
5.3.1.2	Comparative BA & BE Study Reports	R	O

Section	Requirements	G	H
5.3.1.3	In vitro/In vivo Correlation (IV/IVC) study reports	R	O
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human studies	R	R
5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials		
5.3.2.1	Plasma Protein Binding Study Reports		O
5.3.2.2	Reports of Hepatic Metabolism and Drug Interactions studies		O
5.3.2.3	Reports of Studies Using other Human Biomaterials		O
5.3.3	Reports of Human Pharmacokinetic Studies		
5.3.3.1	Healthy Subject PK and Tolerability		
5.3.3.2	Patient PK and Initial Tolerability		
5.3.3.3	Intrinsic Factor PK Study Reports		
5.3.3.4	Extrinsic Factor PK Study Reports		
5.3.3.5	Population PK Study Reports		
5.3.4	Reports of Human Pharmacodynamic (PD) Studies		
5.3.4.1	Healthy Subject PD and PK/PD Study Reports		
5.3.4.2	Patient PD and PK/PD Study Reports		
5.3.5	Reports of Efficacy and Safety Studies		
5.3.5.1	Study reports of Controlled Clinical Studies pertinent to the claimed Indication		
5.3.5.2	Study reports of Uncontrolled Clinical Studies		
5.3.5.3	Reports of Analyses of Data from More than One Study		
5.3.5.4	Other Study Reports		
5.3.6	Reports of Post-Marketing Experience	R	R
5.3.7	Case Report Forms and Individual Patient Listings	R	R
5.4	Literature References	R	R

Appendix B: Electronic Version of the Paper-Based Submission

The electronic version of the paper-based submission is the submission of electronic information by applicants to support a marketing authorization application.

It is formatted as a simple set of electronic files and folders organized into module folders as per the CTD structure.

How to create an electronic version?

1. Create a folder and name it as:

   "Product name – Reference No.".

   For example, "Drug AAA – HG-00253-00-00-00"

2. Inside that folder, create 5 new folders and name it from m1 to m5 (figure 3).

3. Copy the related documents of module 1 and paste it in the folder m1 (figure 4).

4. Repeat step 3 for all modules.

5. After finishing, burn the product file to a CD or a DVD and name it as in step 1.

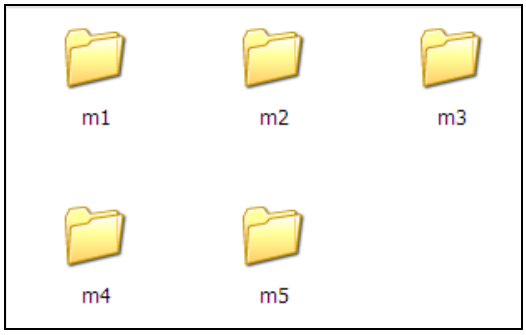

Figure 3: View of the product file after creation of m1 to m5

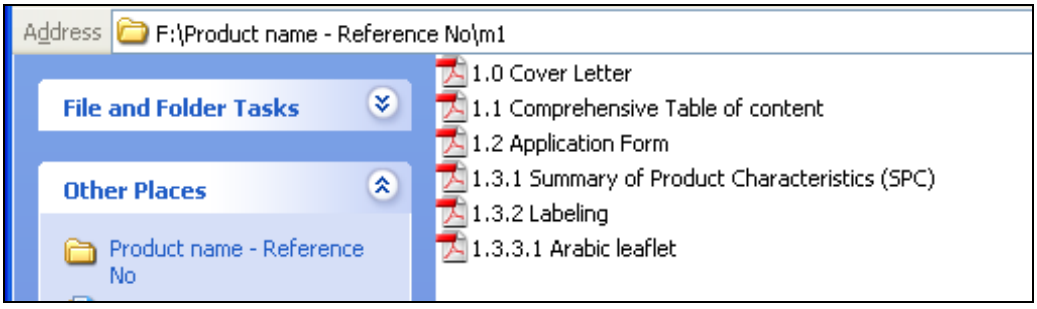

Figure 4: View of the product file after creation of m1

Appendix C: File Formats

General requirements:

Generally, the relevant information must be structured according to the requirements of the Common Technical Document (CTD). The following files formats are accepted:

- PDF
- XML
- Word and RTF[6] file formats, but only in addition to a PDF-file of the same document.
- For graphics: Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), Scalable Vector Graphics (SVG) or Graphic Interchange Format (GIF).

Please refer to the Status of the Common Technical Document Guidelines:

http://www.ich.org/cache/compo/276-254-1.html

Portable Document Format:

PDF is an open, de facto, published format created by Adobe Systems Incorporated (http://www.adobe.com). It is not necessary to use a product from Adobe or from any specific company to produce PDF documents. PDF is accepted as a standard for documents defined in this specification. The following recommendations support the creation of PDF files that agencies can review effectively. To ensure that PDF files can be accessed efficiently, **PDF files should be no larger than 100 megabytes**. Optimize PDF files for fast web view.

The following points can be made in relation to PDF files:

- Files must be legible with PDF version 1.4
- PDF files produced from an electronic source document are highly preferred over PDF files produced from scanned paper, since those 'electronic' PDF files provide the maximum functionality to the reviewers in terms of search and print capabilities, and copy and paste functionality. The overviews/summaries in the CTD Module 2 should always be generated from an electronic source document.
- If scanning is unavoidable, readability and file size must be balanced; the following is recommended: resolution 300 dpi (photographs up to 600 dpi), avoid grayscale or color where possible, use only lossless compression techniques.

[6] Rich Text Format (often abbreviated RTF) is a document file format

- If colors other than black are used, the colored pages must be tested on a black and white printer for acceptable reproduction and legibility prior to submission.
- Print area for pages must fit on an A4 sheet of paper; margins must allow binding in multi-ring binders without affecting readability.
- Landscape-oriented tables must automatically appear in landscape on screen.

Indexing PDF Documents:

The software installed in the SFDA for reviewing use full text indexes to help find specific documents and/or search for text within documents. When a document or group of documents is indexed, all words and numbers in the file and all information stored in the Document

Information fields are stored in special index files that are functionally accessible using the search tools available in Acrobat. Portions of a document that are imaged are not indexed.

These full text indexes should not be confused with a table of contents.

Extensible Markup Language (XML):

XML is developed by a working group of the World Wide Web Consortium (W3C). It is an open-source language developed to improve on previous mark-up languages including Standard Generalized Markup Language (SGML) and Hypertext Markup Language (HTML).

Additional details on XML can be found in the ICH eCTD Specification Document.

Text Searchable Files:

Applicants are requested to ensure that all submissions contain the maximum amount of text searchable content. Documents with searchable text will aid the assessor, or any other user, in searching for specific terms and also in copying and pasting information into another document, such as an assessment report. The SFDA recognizes that not all documents need to be text searchable. This appendix provides some guidance about what must be text searchable and the ways to ensure that files are created appropriately.

Documents that must always be text searchable:

The PDF should be produced wherever possible from a text source, such as MS Word, but if sourced from a scanned original then they **must be** OCR'd.

- Key administrative documents in Module 1 including, the cover letter, application form, SPC, labeling documents
- Any document in Module 2 of the submission (QOS, Preclinical Overview and Summaries, Clinical Overview and Summaries).
- The main body of text of Periodic Safety Update Reports (PSURs)
- The main body of text of Risk Management Plans
- The main body of text and main tables in any preclinical or clinical report required to support the main claim of the application.
- The main body of text in any reports, methods, analytical procedures, etc. supplied in Module 3 of the submission

Documents that do not need to be text searchable:

The PDF should be produced wherever possible from a text source, such as MS Word, but if sourced from a scanned original then there is no need for OCR.

- Any original Certificate of Pharmaceutical Product
- Any original Certificate that confirm that the product is free from BSE/TSE
- Any original GMP certificate
- Any original certificate of analysis
- Any manufacturer's licenses
- Any certificates of suitability
- Any Manufacturing Authorization
- Any literature references sourced from journals, periodicals and books (except when these are used in a bibliographic application so support the main claims of the application).
- Any page with a signature that does not contain other information key to the understanding of the submission
- Applicants should consider providing signatures on separate pages from key text in reports, overviews, etc.

Use of Electronic Signatures:

The use of advanced electronic signatures (digital signatures) will be crucial in achieving pure electronic communication between the pharmaceutical industry and regulatory agencies, particularly for authentication of electronic submissions and documents contained therein. Saudi Arabia is therefore developing a long-term strategy to implement digital signatures. Currently however, the use of digital signatures for electronic submissions within the kingdom of Saudi Arabia is not fully supported and digital signatures should therefore not be used.

Handling Empty or Missing eCTD sections:

For new applications (including generic applications), detailed statements justifying the absence of data or specific CTD sections should be provided in the relevant Quality Overall Summary and/or Non-Clinical/Clinical Overviews (Module 2.3, 2.4, 2.5). Note that placeholder documents highlighting 'no relevant content' should not be placed in the eCTD structure, as these would create a document lifecycle for non-existent documents, and unnecessary complication and maintenance of the eCTD.

NB: for a generic application, note that there is no need to provide a justification for content that is typically absent.

Appendix D: ICH Common Technical Document

Common Technical Document (CTD)

The Common Technical Document is an internationally agreed format for the preparation of a marketing authorization (MA) that is to be submitted to the regulatory authorities in the three ICH regions (USA, EU and Japan) and in some other countries and regions. The CTD provides a common format for the preparation of a well structured dossier. It uses a modular framework described in ICH Topic M4[7]. This guidance document should be read in conjunction with the most recent version of the ICH CTD guidance documents.

It is important to remember that the CTD provides a format for an MAA and does not indicate the content of a dossier and which studies should be performed. Regional and national requirements may affect the content of the dossier; therefore the dossier will not necessarily be identical for all regions.

The CTD is applicable for all types of products (new chemical entities, biologicals, herbals etc.)

The CTD is organized into five modules (figure 4). Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions.

- Module 1: Administrative Information and prescribing Information
- Module 2: Common Technical Document Summaries
- Module 3: Quality
- Module 4: Non-Clinical Study Reports
- Module 5: Clinical Study Reports

[7] http://www.ich.org/

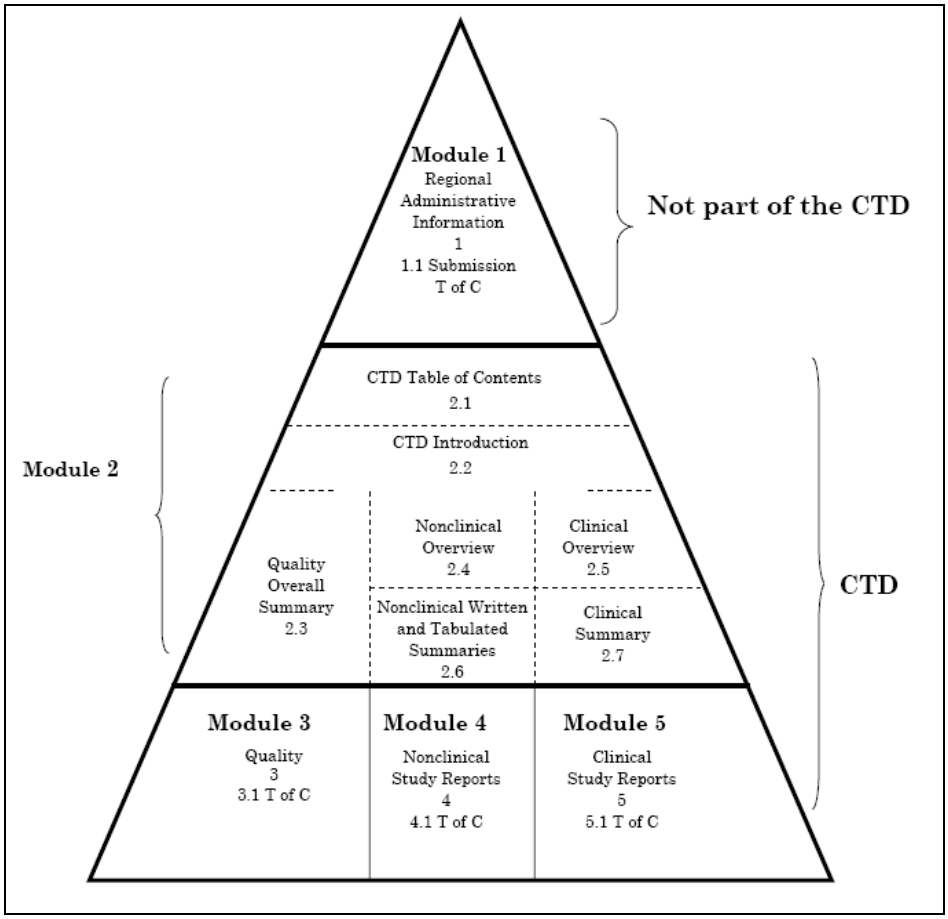

Figure 5: Diagrammatic representation of the organization of the ICH CTD[8]

eCTD

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

The eCTD is an electronic version of the CTD. The structure, folder and file names correspond to those of the CTD. As a submission format, however, it contains additional technical components which enable the lifecycle of individual files in the application, and the lifecycle of the product itself, to be managed.

An eCTD has the following components: Folder structure, Contents (files) and XML backbone.

The folder structure has a hierarchical organization reflecting that of the CTD, and it holds the scientific and technical contents of the eCTD (divided into many files which are the same as those in the non-eCTDs, usually in PDF format).

[8] Source: adapted from the ICH guideline……

The XML backbone is recognisable as 'index.xml' at the root level of the submission folder of an eCTD and provides two useful functions:

- It provides a hyperlinked table of contents of the entire submission when viewed in a web browser with a suitable style sheet
- It provides descriptive information ('metadata') on the files that make up the actual contents of the eCTD.

Appendix E: Target Performance Timelines

Target performance timelines from the date of acceptance to SFDA decision, excluding the stop-clock for various submission types are as follows:

The timelines stated (in working days) are subject to change.

Process	Total Performance Target
Marketing Authorization Application for Generics	165 days
Marketing Authorization Application for NCEs	290 days
Marketing Authorization Application for Biologicals	290 days
Marketing Authorization Application for Radiopharmaceuticals	290 days
Marketing Authorization Application for Veterinary drugs	195 days
Marketing Authorization Application for Herbal products	155 days
Renewal of Marketing Authorization	30 days
Variation to a Marketing Authorization Type I: Notifiable Change	30 days
Variation to a Marketing Authorization Type II: Supplemental to MA	165 days

Appendix F: Required Quantities of Samples

The following table shows the required quantities of the samples for different sample types.

No.	Sample Type	Volume	Quantity
1	Tablets	-	100 tablets
2	Capsule	-	100 capsules
3	Syrup	> 250 mL	6-8 packs
4	Solution	250-500 mL	6 packs
5	Solution	5-10 L	2 packs
6	Antiseptic	1 L	6 packs
7	Antiseptic	5 L	2 packs
8	Drops	15 mL	15 packs
9	Ointment & Creams	-	15 packs
10	Raw materials	-	2 packs
12	Ampoules, Vials & PFS	0.5 mL	25 packs
13	Ampoules, Vials & PFS	1 mL	20 packs
14	Ampoules, Vials & PFS	2-5 mL	15 packs
15	Bottles	≥ 5 mL	6 bottles
16	BCG vaccine	-	50 packs
17	Blood bags	-	8 bags
18	Infusion sets	-	6 packs

Notes:

- The SFDA has the right to ask for additional quantities as needed.
- The SFDA has the right to ask for analysis tools and standard materials as needed.

Appendix G: References

SFDA Reference Documents:

- Regulatory Framework for Drug Approvals *(version 4)*
- Bioequivalence Guidelines
- Stability Guidelines
- SPC, Labeling and PIL guidelines *(published soon)*
- SA Module 1 Specification *(published soon)*

The latest versions of SFDA's guidance documents are available on the website at the following address:

http://www.sfda.gov.sa/En/Drug/Topics/Regulations+-+Guidelines.htm

ICH Reference Documents:

M4 : The Common Technical Document

- Organization of The Common Technical Document for the Registration of Pharmaceuticals for Human Use
- Implementation Working Group – Questions & Answers (R3)
- Electronic Common Technical Document Specification (version 3.2)
- The Common Technical Document for The Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1)
- The Common Technical Document for The Registration of Pharmaceuticals for Human Use: Safety – M4S(R2)
- The Common Technical Document for The Registration of Pharmaceuticals for Human Use: Efficacy – M4E(R1)

These documents and more are found at the ICH website at the following address:

http://www.ich.org/

Appendix H: Contact Address

Saudi Food and Drug Authority – Drug Sector

3292 Northern Ring Road – An nafal District

Riyadh 13312 – 6288

Kingdom of Saudi Arabia

Tel: +966-1-275- 9222 extensions: 1302 or 5302

Fax: +966-1-275-7195

e-mail: Drug-Dept@sfda.gov.sa

Appendix I: Price List

Product trade name		**Package size**	
Strength/unit		**Ex-Factory price**	
Dosage form		**COO Wholesale price**	
Company name		**COO public price**	
Nationality		**CIF to SA**	

The other prices in the countries where the product is marketed

No.	Country	COO	Currency	Package size	Ex-factory price	CIF price	Public price
1	Algeria						
2	Australia						
3	Argentina						
4	Bahrain						
5	Belgium						
6	Canada						
7	Cyprus						
8	Denmark						
9	Egypt						
10	Finland						
11	France						
12	Germany						
13	Greece						
14	Netherlands						
15	Hungary						
16	Ireland						
17	Italy						
18	Japan						
19	Jordan						
20	Kuwait						
21	New Zealand						
22	Norway						
23	Oman						
24	Portugal						
25	Lebanon						
26	Spain						
27	Sweden						
28	Switzerland						
29	U.A.E.						
30	U.K.						

Appendix J: Cover Letter

سعادة نائب الرئيس التنفيذي للهيئة العامة للغذاء والدواء لشؤون الدواء **سلمه الله**

السلام عليكم ورحمة الله وبركاته، ، ،

نتقدم إلى سعادتكم بطلب الحصول على رخصة تسويق مستحضر الموضحة بياناته أدناه، علما بأنه تم إرفاق جميع البيانات والدراسات المطلوبة مع هذا الخطاب:

Trade Name		**الاسم التجاري**
Generic Name		**الاسم العلمي**
Strength		**التركيز**
Dosage Form		**الشكل الصيدلاني**
manufacturer		**الشركة الصانعة**
Marketing Company		**الشركة المسوقة**

وتقبلوا سعادتكم خالص التحية والتقدير، ، ،

مدير شركة.....

Appendix K: Laboratory Samples Form

Trade Name		الاسم التجاري
Generic Name		الاسم العلمي
Strength		التركيز
Dosage Form		الشكل الصيدلاني
Storage condition		شروط التخزين
Sample Quantity		عدد العينات للتحليل
Marketing Company		الشركة المسوقة
Manufacturer		الشركة الصانعة
Expiry Date		تاريخ انتهاء الصلاحية
Batch No.		رقم التشغيلة

Appendix L: Abbreviation and Acronyms

COO	Country of Origin
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
MA	Marketing Authorization
MAA	Marketing Authorization Application
NCE	New Chemical Entity
PFS	Prefilled syringe
PIL	Patient Information Leaflet
SA	Saudi Arabia
SFDA	Saudi Food and Drug Authority
SPC	Summary of Product Characteristics