Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

12 August 2013

FDA CIRCULAR
No. 2013-019

SUBJECT: **Organization of the ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceutical Products for Human Use**

I. BACKGROUND/RATIONALE

Pursuant to Administrative Order No. 2013-0021 known as the "Adoption of the Association of Southeast Asian Nations (ASEAN) Common Technical Dossier (ACTD) and Common Technical Requirements (ACTR) for the Registration of Pharmaceutical Products for Human Use," the Center for Drug Regulation and Research (CDRR), in enhancing public health and welfare by providing faster access to and increasing availability of quality, safe, and efficacious pharmaceutical products, hereby stipulates the format for the preparation of well-structured ACTD applications.

This Circular intends to provide assistance to stakeholders in the submission of applications with an organized structure following the ACTD format, for the documentation of data on the administrative, quality, non-clinical and clinical aspects of pharmaceutical products for human use that will be submitted to the CDRR for registration.

This Circular shall apply to all manufacturers, traders, and distributors (e.g. exporters, importers, and wholesalers) of pharmaceutical products. However, this shall not cover manufacturers, traders, and distributors of single and multiple-component vitamin and mineral products, traditional medicines, over-the-counter preparations, household remedies, medical gases, and veterinary products.

II. IMPLEMENTING DETAILS

A. Format

The following are the specific requirements with regards to the format of the dossier to be submitted:

1. Text and tabulated data should be margined in a format that allows the document to be printed on an A4 paper. The left-hand margin should be 1.5" with all other margins at 1". No information should be obscured by the method of binding.

2. For narrative text, the recommended font style is Times New Roman at 12-point font size.
3. Pagination shall cover all sheets included in the dossier and shall commence on the first page and terminate on the last page of every section.
4. Acronyms and abbreviations should be defined the first time they are used in each part.
5. Documents submitted should be placed in a green folder/binder with dividers or tabs for every section/part. This should be enclosed in an expanding plastic envelope.
6. In addition to the hard copy of the requirements, applicant companies shall submit an electronic of the application (in PDF searchable format and at least 300 dpi) on a DVD-R. The DVD-R shall be placed on a green hard-case of 14 cm x 12.5 cm x 1 cm size.

B. Organization of the Dossier

The registration dossier is organized into four parts as follows:

Part I: Administrative Data and Product Information
Sec. A Introduction
Sec. B Table of Contents
1. Application Form
2. Letter of Authorization (where applicable)
3. Certifications
4. Labeling
5. Product Information

Sec. C Guidance on the Administrative Data and Product Information
1. Application Form
2. Letter of Authorization (where applicable)
3. Certifications
For contract manufacturing:
a. License of pharmaceutical industries and contract manufacturer
b. Contract manufacturing agreement
c. GMP certificate of contract manufacturer
For manufacturing "under-license"
a. License of pharmaceutical industries
b. GMP certificate of the manufacturer
c. Copy of "under-license" agreement
For locally manufactured
a. License of pharmaceutical industries
b. GMP certificate (country specific)
For imported products
a. License of pharmaceutical industries/importer/wholesaler (country specific)

b. Certificate of Pharmaceutical Product issued by the competent authority in the country of origin according to the current WHO format

c. Site Master File of the manufacturer (unless previously submitted within the last 2 years) (country specific)

4. Labeling
5. Product Information
   - 5.1. Package Insert
   - 5.2. Summary of Product Characteristics (Product Data Sheet)
   - 5.3. Patient Information Leaflet (PIL)

Part II: Quality

Sec. A Table of Contents

Sec. B Quality Overall Summary

Sec. C Body of Data

Drug Substance (S)

S 1 General Information
- S 1.1. Nomenclature
- S 1.2. Structural Formula
- S 1.3. General Properties

S 2 Manufacture
- S 2.1. Manufacturer(s)
- S 2.2. Description of Manufacturing Process and Process Controls
- S 2.3. Control of Materials
- S 2.4. Control of Critical Steps and Intermediates
- S 2.5. Process Validation and/or Evaluation
- S 2.6. Manufacturing Process Development

S 3 Characterization
- S 3.1. Elucidation of Structure and Characteristics
- S 3.2. Impurities

S 4 Control of Drug Substance
- S 4.1. Specifications
- S 4.2. Analytical Procedures
- S 4.3. Validation of Analytical Procedures
- S 4.4. Batch Analyses
- S 4.5. Justification of Specifications

S 5 Reference Standards or Materials

S 6 Container Closure System

S 7 Stability

Drug Product (P)

P 1 Description and Composition

P 2 Pharmaceutical Development

P 2.1. Information on Development Studies
P 2.2. Components of the Drug Product
P 2.2.1. Active Ingredients
P 2.2.2. Excipients
P 2.3. Finished Product
P 2.3.1. Formulation Development
P 2.3.2. Overages
P 2.3.3. Physicochemical and Biological Properties
P 2.4. Manufacturing Process Development
P 2.5. Container Closure System
P 2.6. Microbiological Attributes
P 2.7. Compatibility
P 3 Manufacture
P 3.1. Batch Formula
P 3.2. Manufacturing Process and Process Control
P 3.3. Controls of Critical Steps and Intermediates
P 3.4. Process Validation and/or Evaluation
P 4 Control of Excipients
P 4.1. Specifications
P 4.2. Analytical Procedures
P 4.3. Excipients of Human and Animal Origin
P 4.4. Novel Excipients
P 5 Control of Finished Product
P 5.1. Specifications
P 5.2. Analytical Procedures
P 5.3. Validation of Analytical Procedures
P 5.4. Batch Analyses
P 5.5. Characterization of Impurities
P 5.6. Justification of Specifications
P 6 Reference Standards or Materials
P 7 Container Closure System
P 8 Product Stability
P 9 Product Interchangeability

Part III: Nonclinical Document
Sec. A Table of Contents
Sec. B Nonclinical Overview
1. General Aspect
2. Content and Structural Format
Sec. C Nonclinical Written and Tabulated Summaries
1. Nonclinical Written Summaries
1.1. Introduction
1.2. General Presentation Issues
2. Content of Nonclinical Written and Tabulated Summaries
2.1. Pharmacology

2.1.1. Written Summary
2.1.1.1. Primary Pharmacodynamics
2.1.1.2. Secondary Pharmacodynamics
2.1.1.3. Safety Pharmacology
2.1.1.4. Pharmacodynamic Drug Interactions
2.1.2. Tabulated Summary
2.2. Pharmacokinetics
2.2.1. Written Summary
2.2.1.1. Absorption
2.2.1.2. Distribution
2.2.1.3. Metabolism
2.2.1.4. Excretion
2.2.1.5. Pharmacokinetic Drug Interaction (Nonclinical)
2.2.2. Tabulated Summary
2.3. Toxicology
2.3.1. Written Summary
2.3.1.1. Single-Dose Toxicity
2.3.1.2. Repeat-Dose Toxicity
2.3.1.3. Genotoxicity
2.3.1.4. Carcinogenicity
2.3.1.5. Reproductive and Developmental Toxicity
2.3.1.5.1. Fertility and Early Embryonic Development
2.3.1.5.2. Embryo-Foetal Development
2.3.1.5.3. Prenatal and Postnatal Development
2.3.1.6. Local Tolerance
2.3.1.7. Other Toxicity (if available)
2.3.2. Tabulated Summary
3. Nonclinical Tabulated Summaries

Sec. D Nonclinical Study Reports
1. Table of Contents
2. Pharmacology
2.1. Written Study Reports
2.1.1. Primary Pharmacodynamics
2.1.2. Secondary Pharmacodynamics
2.1.3. Safety Pharmacology
2.1.4. Pharmacodynamic Drug Interactions
3. Pharmacokinetics
3.1. Written Study Reports
3.1.1. Analytical Methods and Validation Reports
3.1.2. Absorption
3.1.3. Distribution

3.1.4. Metabolism
3.1.5. Excretion
3.1.6. Pharmacokinetic Drug Interaction (Nonclinical)
3.1.7. Other Pharmacokinetic Studies

4. Toxicology
4.1. Written Study Reports
4.1.1. Single-Dose Toxicity
4.1.2. Repeat-Dose Toxicity
4.1.3. Genotoxicity
4.1.3.1. In-vitro Reports
4.1.3.2. In-vivo Reports
4.1.4. Carcinogenicity
4.1.4.1. Long Term Studies
4.1.4.2. Short or Medium Term Studies
4.1.4.3. Other Studies
4.1.5. Reproductive and Developmental Toxicity
4.1.5.1. Fertility and Early Embryonic Development
4.1.5.2. Embryo-Foetal Development
4.1.5.3. Prenatal and Postnatal Development
4.1.5.4. Studies in which the Offspring are Dosed and/or further Evaluated
4.1.6. Local Tolerance
4.1.7. Other Toxicity Studies (if available)
4.1.7.1. Antigenicity
4.1.7.2. Immunotoxicity
4.1.7.3. Dependence
4.1.7.4. Metabolites
4.1.7.5. Impurities
4.1.7.6. Other

Sec. E List of Key Literature References

Part IV: Clinical Document
Sec. A Table of Contents
Sec. B Clinical Overview
1. Product Development Rationale
2. Overview of Biopharmaceutics
3. Overview of Clinical Pharmacology
4. Overview of Efficacy
5. Overview of Safety
6. Benefits and Risks Conclusions

Sec. C Clinical Summary
1. Summary of Biopharmaceutic Studies and Associated Analytical Method
1.1. Background and Overview

1.2. Summary of Results of Individual Studies
1.3. Comparison and Analyses of Results Across Studies
Appendix 1
2. Summary of Clinical Pharmacology Studies
2.1. Background and Overview
2.2. Summary of Results of Individual Studies
2.3. Comparison and Analyses of Results Across Studies
2.4. Special Studies
Appendix 2
3. Summary of Clinical Efficacy
3.1. Background and Overview of Clinical Efficacy
3.2. Summary of Results of Individual Studies
3.3. Comparison and Analyses of Results Across Studies
3.4. Analysis of Clinical Information Relevant to Dosing Recommendations
3.5. Persistence of Efficacy and/or Tolerance Effects
Appendix 3
4. Summary of Clinical Safety
4.1. Exposure to the Drug
4.2. Adverse Events
4.3. Clinical Laboratory Evaluations
4.4. Vital Signs, Physical Finding, and Other Observations Related to Safety
4.5. Safety in Special Groups and Situations
4.6. Post-Marketing Data
Appendix 4
5. Synopses of Individual Studies

Sec. D Tabular Listing of All Clinical Studies

Sec. E Clinical Study Reports (if applicable)

1. Reports of Biopharmaceutic Studies
1.1. BA Study Reports
1.2. Comparative BA or BE Study Reports
1.3. *In vitro-In vivo* Correlation Study Reports
1.4. Reports of Bioanalytical and Analytical Methods for Human Studies
2. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials
2.1. Plasma Protein Binding Study Reports
2.2. Reports of Hepatic Metabolism and Drug Interaction Studies
2.3. Reports of Studies Using Other Human Biomaterials
3. Reports of Human Pharmacokinetic (PK) Studies
3.1. Healthy Subject PK and Initial Tolerability
3.2. Patient PK and Initial Tolerability Study Reports
3.3. Population PK Study Reports
4. Reports of Human Pharmacodynamic (PD) Studies

4.1. Healthy Subject PD and PK/PD Study Reports
4.2. Patient PD and PK/PD Study Reports

5. Reports of Efficacy and Safety Studies
   5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
   5.2. Study Reports of Uncontrolled Clinical Studies
   5.3. Reports of Analyses of Data from more than One Study, Including any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses
   5.4. Other Clinical Study Reports
6. Reports of Post-Marketing Experience
7. Case Report Forms and Individual Patient Listing

Sec. F List of Key Literature References

The CDRR shall allow flexibility, in terms of requirements, between the ACTD and ICH CTD. The following are the differences of the ICH CTD and ACTD structure:

Documents	**Location**	
	ACTD	**ICH CTD**
Administrative Documents and Product Information	Part I	Module 1
Common Technical Document Overview and Summaries	Incorporated in Parts II, III, and IV	Module 2
Quality Documents	Part II	Module 3
Non-Clinical Documents	Part III	Module 4
Clinical Documents	Part IV	Module 5

III. REPEALING CLAUSE/SEPARABILITY CLAUSE

Provisions on previous circulars and memoranda that are inconsistent with this issuance are hereby withdrawn, repealed, and/or revoked accordingly.

IV. EFFECTIVITY

This Circular shall take effect immediately.

KENNETH Y. HARTIGAN-GO, MD
Acting Director IV, FDA

ANNEX

The following tables present the organization of the levels in the ACTD hierarchy at which document/files should be placed and whether single or multiple documents are appropriate at each point. This describes all sections of ACTD but for individual submissions all sections might not be applicable.

<table>
<tr><td colspan="4">Granularity Document</td></tr>
<tr><td rowspan="12">Part I</td><td>Sec. A</td><td></td><td></td></tr>
<tr><td rowspan="5">Sec. B</td><td>1.</td><td></td></tr>
<tr><td>2.</td><td></td></tr>
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<tr><td>4.</td><td></td></tr>
<tr><td>5.</td><td></td></tr>
<tr><td rowspan="6">Sec. C</td><td>1.</td><td></td></tr>
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<tr><td>3.</td><td></td></tr>
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Granularity Document					
Part II [Note 1]	Sec. A	TOC			
	Sec. B				
	Sec. C	1. (S) [Note 2]	S.1.	S.1.1.	
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			S.2.	S.2.1.	
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				S.2.3.	
				S.2.4.	
				S.2.5.	
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			S.3.	S.3.1.	
				S.3.2.	
			S.4.	S.4.1.	
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		2. (P) [Note 3]	P.1.		
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			P3	P.3.1.	
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			P5	P.5.1.	
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	Sec. D				

TOC - Table of Contents

1 - When relevant information is changed at any point in the product's lifecycle, applicant companies should follow the requirements in the ASEAN Variation Guidelines for Pharmaceutical Products.

2 - 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.

3 - For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate "P", as appropriate.

Granularity Document							
Part III	Sec. A	TOC					
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	Sec. C	1.		1.1.			
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						2.1.1.2.	
						2.1.1.3.	
						2.1.1.4.	
					2.1.2.		
				2.2.	2.2.1.	2.2.1.1.	
						2.2.1.2.	
						2.2.1.3.	
						2.2.1.4.	
					2.2.2.		
				2.3.	2.3.1.	2.3.1.1.	
						2.3.1.2.	
						2.3.1.3.	
						2.3.1.4.	
						2.3.1.5.	2.3.1.5.1.
							2.3.1.5.2.
							2.3.1.5.3.
						2.3.1.6.	
						2.3.1.7.	
					2.3.2.		
		3.					
	Sec. D	1.					
		2.	2.1.	2.1.1.	Studies Note 1		
				2.1.2.	Studies Note 1		
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				2.1.4.	Studies Note 1		
		3.	3.1.	3.1.1.	Studies Note 1		
				3.1.2.	Studies Note 1		
				3.1.3.	Studies Note 1		
				3.1.4.	Studies Note 1		
				3.1.5.	Studies Note 1		
				3.1.6.	Studies Note 1		
				3.1.7.	Studies Note 1		
		4.	4.1.	4.1.1.	Studies Note 1		
				4.1.2.	Studies Note 1		
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					4.1.3.2.	Studies Note 1	
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					4.1.7.2.	Studies Note 1	

					4.1.7.3.	Studies [Note 1]	
					4.1.7.4.	Studies [Note 1]	
					4.1.7.5.	Studies [Note 1]	
					4.1.7.6.	Studies [Note 1]	
	Sec. E						

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1 - Typically, a single document should be provided for each study report included in Part III. Applicant companies can choose to submit the report as more than one document where the study report is large (e.g., a carcinogenicity study). In this case, the text portion of the report should be one document and the appendices can be one or more documents. When relevant information is changed at any point in the product's lifecycle, applicant companies should follow the requirements in the ASEAN Variation Guidelines for Pharmaceutical Products.

Granularity Document				
Part IV	Sec. A	TOC		
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			Appendix 1	
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			Appendix 2	
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			Appendix 4	
		5.		
	Sec. D			
	Sec. E	1.	1.1.	Studies Note 1
			1.2.	Studies Note 1
			1.3.	Studies Note 1
			1.4.	Studies Note 1
		2.	2.1.	Studies Note 1
			2.2.	Studies Note 1
			2.3.	Studies Note 1
		3.	3.1.	Studies Note 1
			3.2.	Studies Note 1
			3.3.	Studies Note 1
		4.	4.1.	Studies Note 1
			4.2.	Studies Note 1
		5.	5.1.	Studies Note 1
			5.2.	Studies Note 1
			5.3.	Studies Note 1
			5.4.	Studies Note 1
		6.		
		7.	Studies Note 1	
	Sec. F			

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1 - The applicants should ordinarily provide the study reports as multiple documents (a synopsis, a main body of the study report and appropriate appendices). When relevant information is changed at any point in the product's lifecycle, applicant companies should follow the requirements in the ASEAN Variation Guidelines for Pharmaceutical Products.