China Registration

Daewoong Pharmaceutical Co., Ltd

Regulatory Affairs
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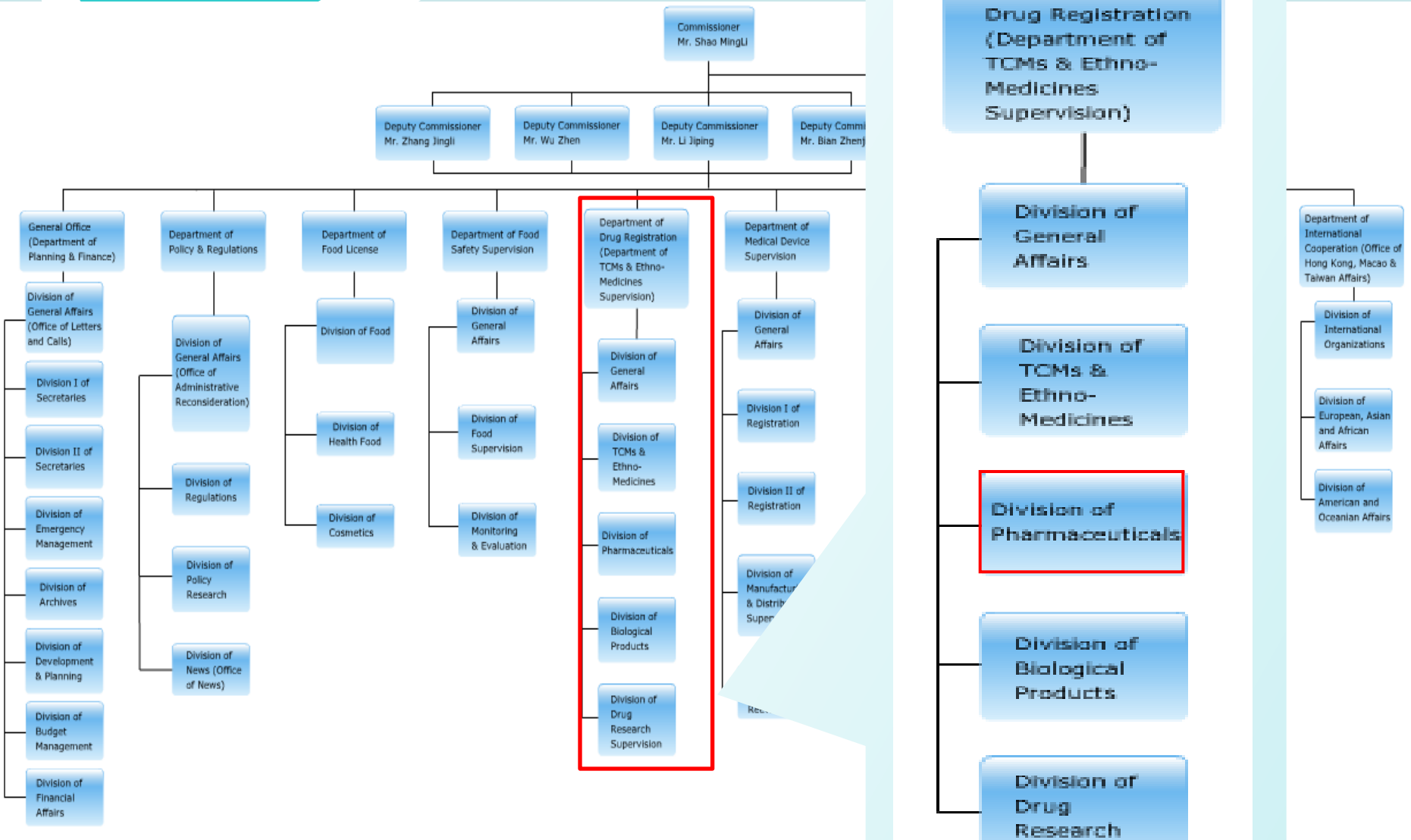
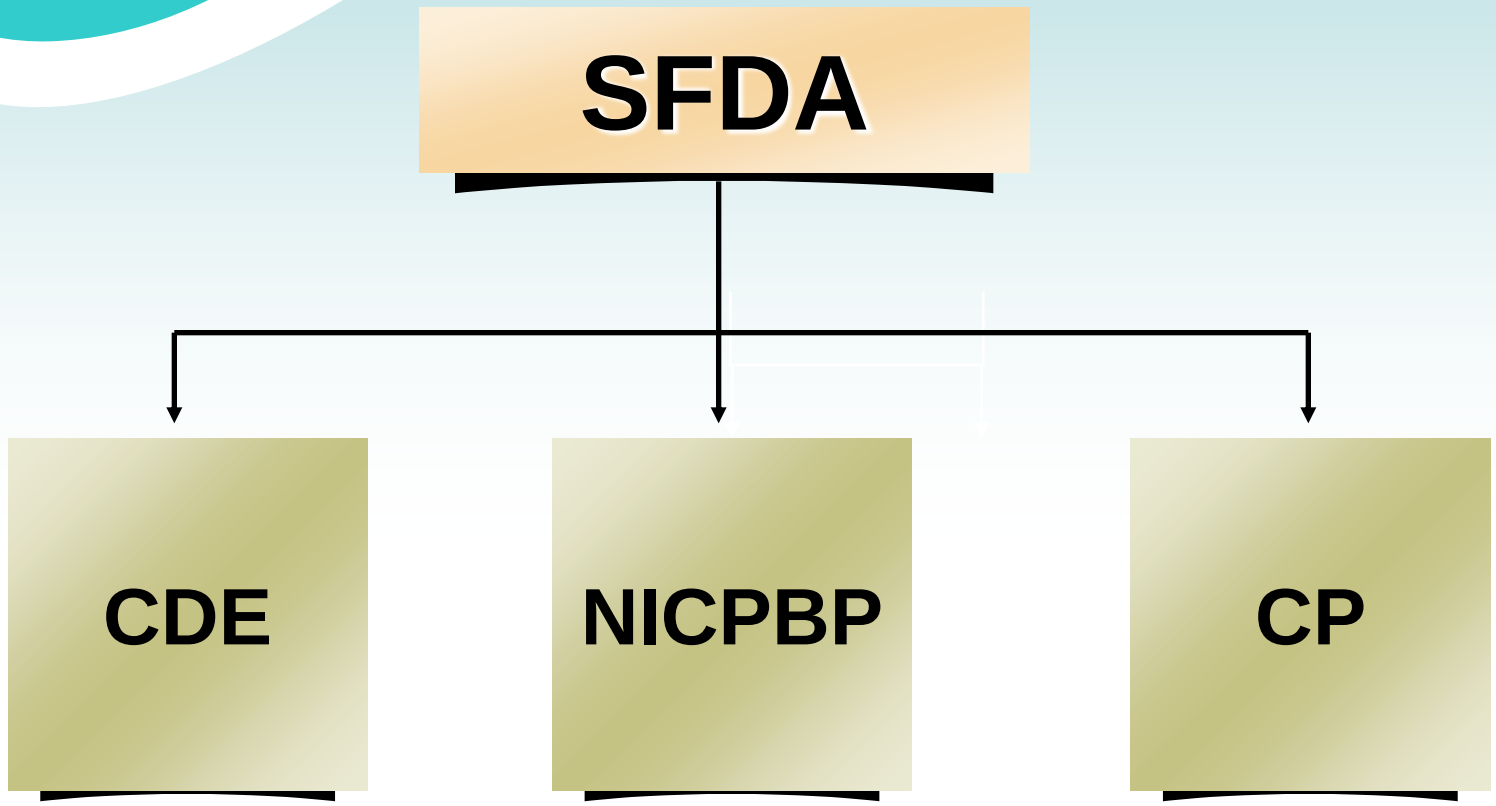
Contents

1. Drug registration or



1. Drug registration organization



CDE: Center for Drug Evaluation

NICPBP: National Institute for the control of pharmaceutical and biological product

CP: Chinese Pharmacopeia Committee

1. Drug registration organization

1. SFDA (State Food and Drug Administration)

1) Similar to KFDA
2) Responsible for the **import drug registration**

2. Local SFDA

1) Similar to Regional KFDA
2) Responsible for the local drug registration
   local drug registration accept the application, and site verif ication (domestic company)
   but decision of registration is made by SFDA.

1. Drug registration organization

3. CDE (Center for Drug Evaluation)
Technical evaluation in SFDA
(CMC, Non-clinical, Clinical part evaluation)

4. CICPBP/NICPBP
Coast/National Institute for the Control of Pharmaceutical and Biological Products - Quality verification
(Specification Review)

5. CP (Chinese Pharmacopeia Committee)
Work about writing CP

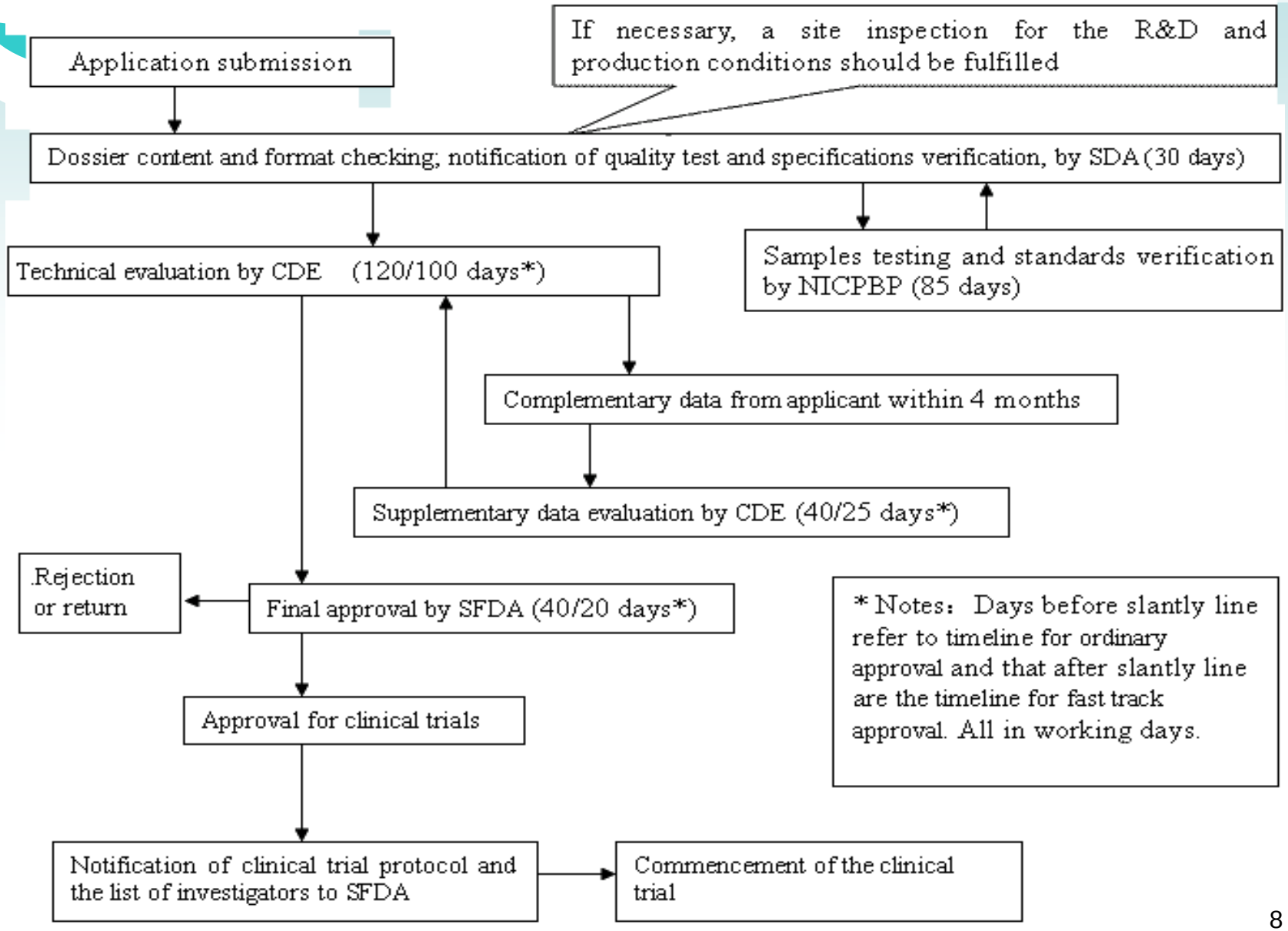
2. Application and approval procedure

Documentation → IND application → Supplementary data submission → Clinical Trial Permission → BE/Clinical study → NDA application → Supplementary data submission → Import Drug License → ETC: Reimbursement price application / OTC: OTC committee

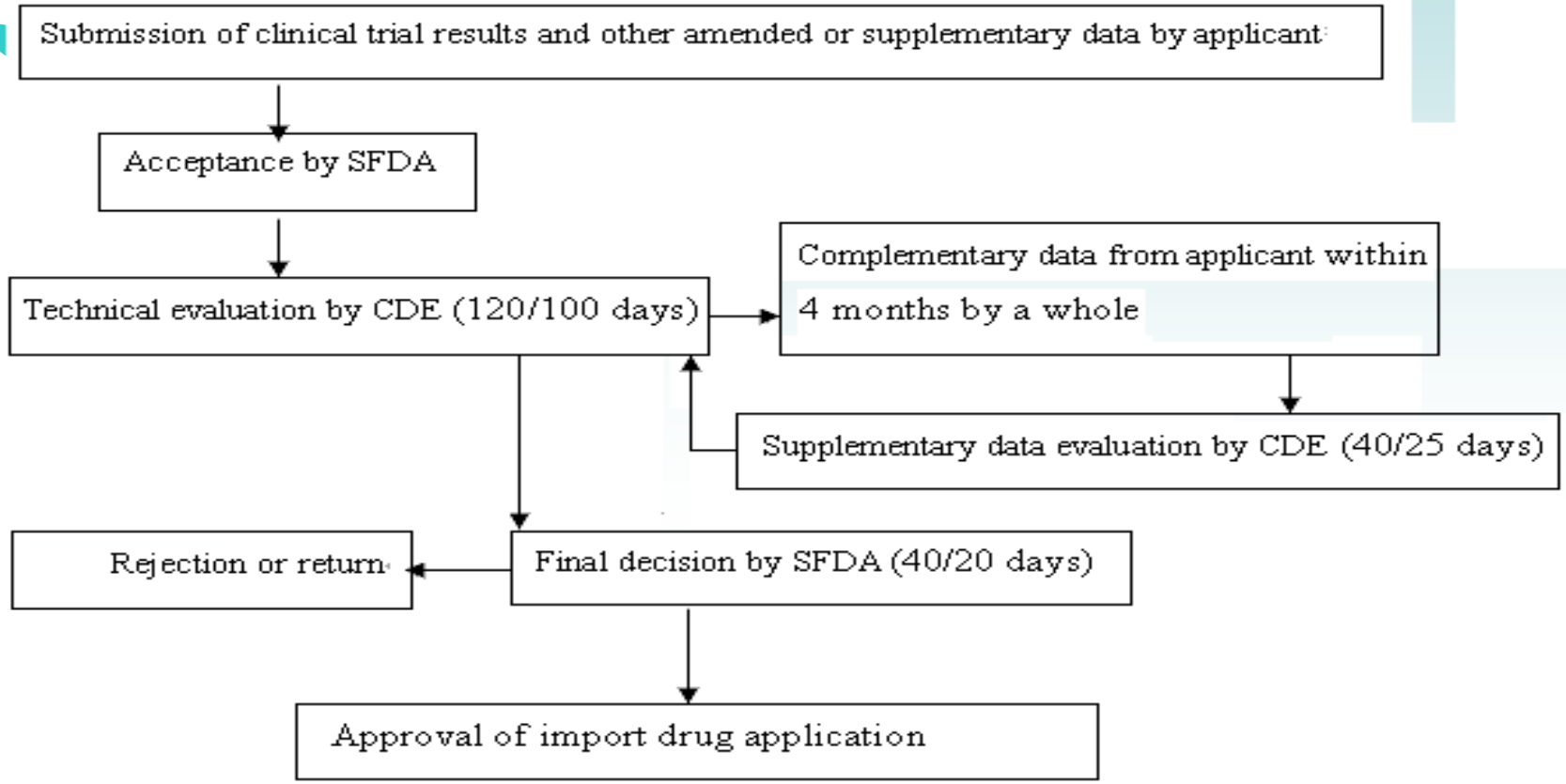
Phase	Timeline
Application for Clinical Trial Approval (IND)	8-10 months By SFDA
Conduct clinical trial in China	This time window depends on trial protocol design and treatment duration etc.
Application for the Import Drug License after clinical trial (NDA)	10-12 months By SFDA
ETC reimbursement price application OTC committee	6 months 3 months

Application Fee: USD 6,662, Quality verification Fee: USD 3,000-5,000

2.1 Procedure (1) - IND



2.2 Procedure (2) -NDA

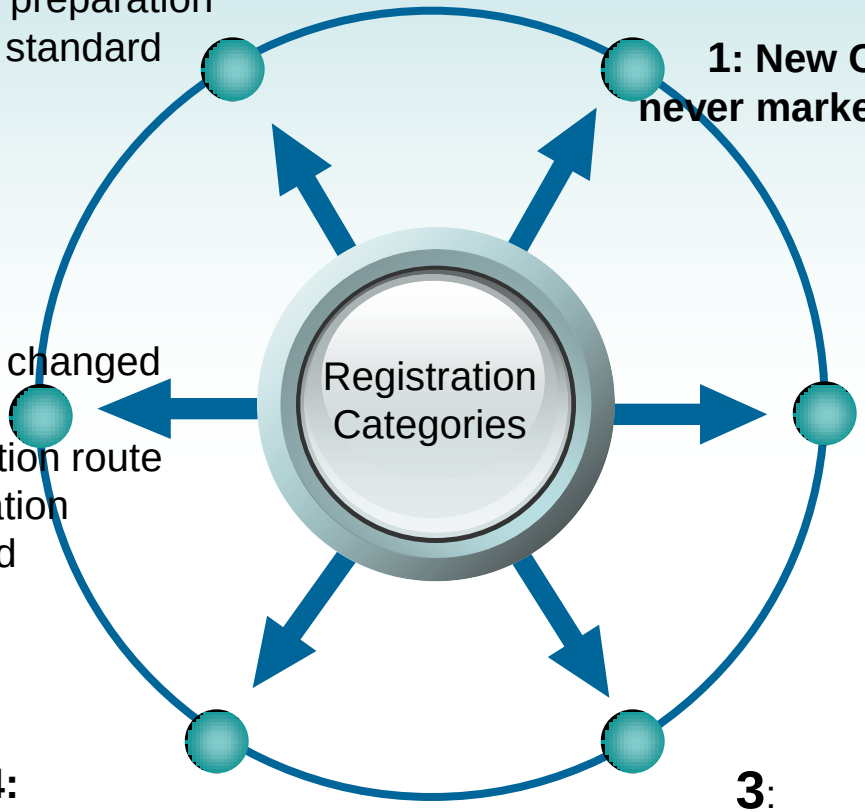


* Notes: Days before slantly line refer to timeline for ordinary approval and that after slantly line are the timeline for fast track approval. All in working days.

3. Registration categories

6: Drug substance or preparation
Following national standard

1: New Chemical Entity
never marketed in any country



5: Drug preparation with changed dose form
No change of administration route
The original preparation already approved
In china

2: Drug preparation with changed administration route
not marketed in any country

4:
Drug substance and its preparation with
Changed acid or alkaline radicals,
But without any pharmacological change,
The origin drug entity already approved in china

3:
Drug marketed ex-China

3.1 Classification 1 & 2

1. New chemical entity never marketed in any country.
1.1 Drug substance and its preparations made by synthesis or semi-synthesis.
1.2 Chemical monomer (including drug substance and preparation) extracted from natural sources or by fermentation.
1.3 Optical isomer (including drug substance and preparation) obtained by chiral separation or synthesis.
1.4 Drug with fewer components derived from marketed multi-component drug.
1.5 New combination products.
1.6 A preparation already marketed in China but with a newly added indication not yet approved in any country.

2. Drug preparation with changed administration route and not marketed in any country

- **Clinical study**

Phase I : 20-30, Phase II: 100, Phase III: 300, Phase IV: 2000

3.2 Classification 3 & 4

3. Drug marketed ex-China, including:
3.1 Drug substance and its preparations, and / or with changed dose form, but no change of administration route.
3.2 Combination preparations, and / or with changed dose form, but no change of administration route.
3.3. Preparations with changed administration route and marketed ex-China.
3.4 A preparation already marketed in China but with a newly added indication approved ex-China.

4. Drug substance and its preparation with changed acid or alkaline radicals (or metallic elements), but without any pharmacological change, and the original drug entity already approved in China.

- **Comparative Clinical study (100 pairs)**
- **Bioequivalence Study (18~24 subject)**
- **PK (18~24 subject) & Comparative Clinical study (100 pairs)**

3.3 Classification 5 & 6

5. Drug preparation with changed dose form, but no change of administration route, and the original preparation already approved in China

- **Oral solid preparation: Bioequivalence Study (18~24 subjects)**
- **Oral solid preparation couldn't conduct BE or non-oral solid preparation: Comparative Clinical study (100 pairs)**
- **Sustained/ controlled release preparation: PK(18~24 subjects & Comparative Clinical study (100 pairs)**
- **Injection (identical with the original dosage form): Clinical study can be exempted.**

6. Drug substance or preparation following national standard.

- **Bioequivalence Study (18~24 subject)**

3.4 Comparative clinical study

Comparative drug for clinical study

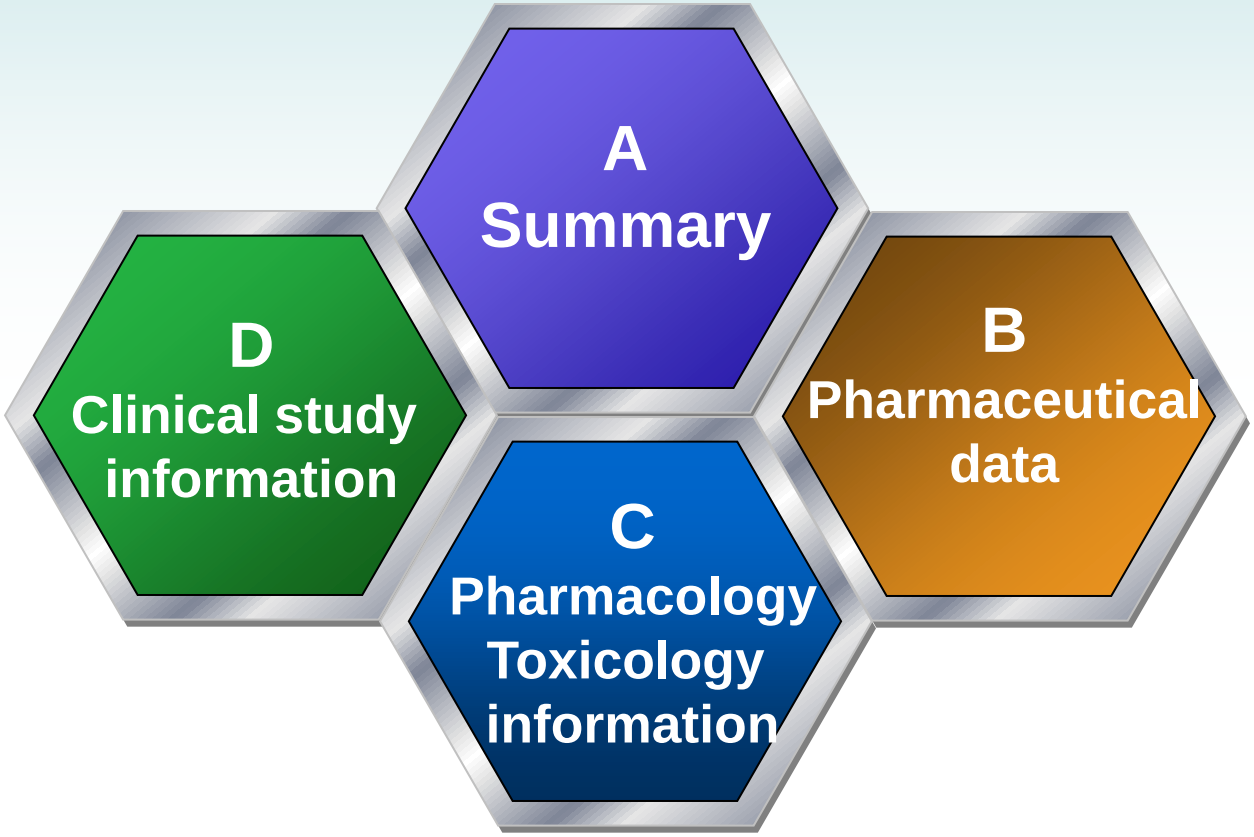
1. Already marketed in China
2. If the comparative drug must be imported – approval from SFDA

- Drug from the original manufacturer
- The same drug of definite clinical test data
- Drug of the same active substance and route of administration but different dosage form
- Other drug of similar mechanism of action effect and the same indication

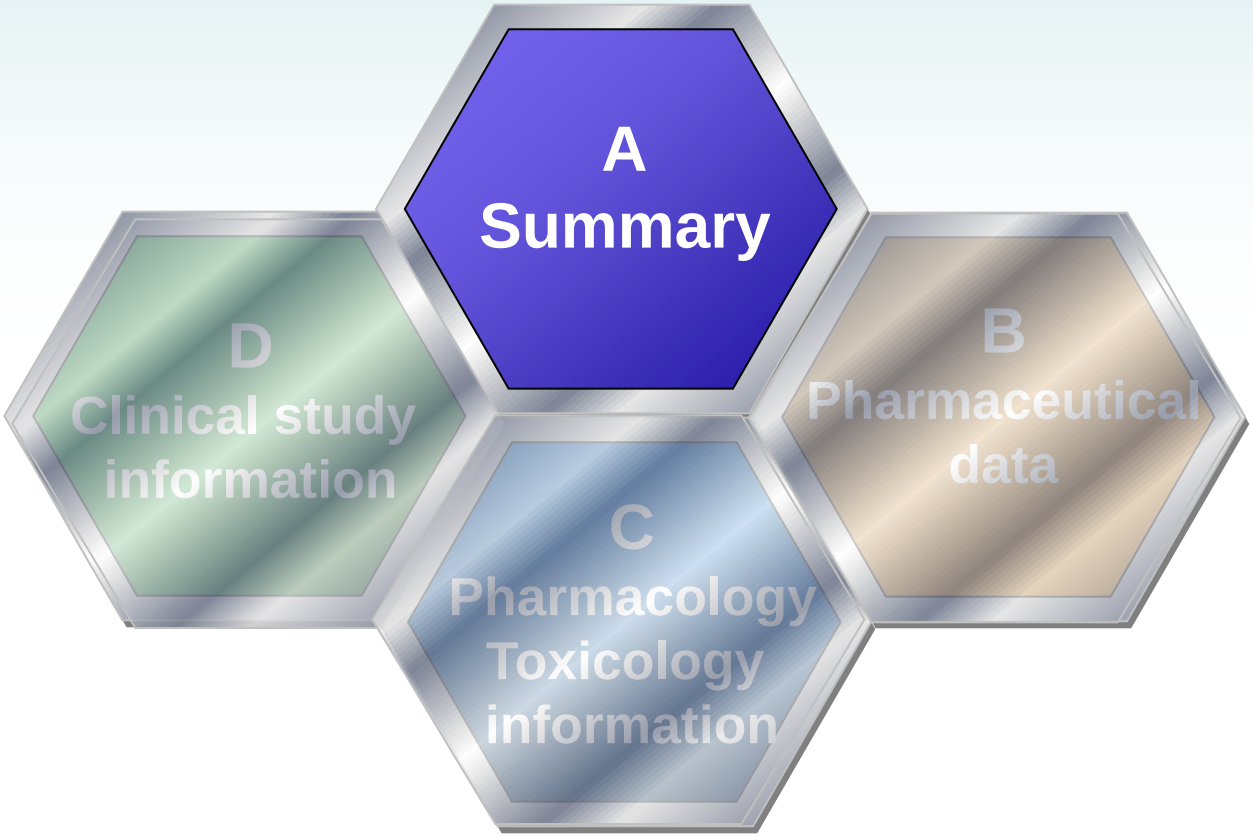
Fee of clinical study

- Normally 5000 (CNY)/case : 800,000 KRW/case
- 240 cases: about 200,000,000 KRW

4. Application dossier items



4.A. Summary



No	Categories					
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2	+	+	+	+	+	+
3	+	+	+	+	+	+
4	+	+	+	+	+	+
5	+	+	+	+	+	+
6	+	+	+	+	+	+

4.A. Summary

1) Name of the product
Generic name, Trade name, chemical name,
chemical structure, Molecular formula, molecular weight

2) Certified Documents
CPP, GMP, Patent guarantee, Letter of Authorization

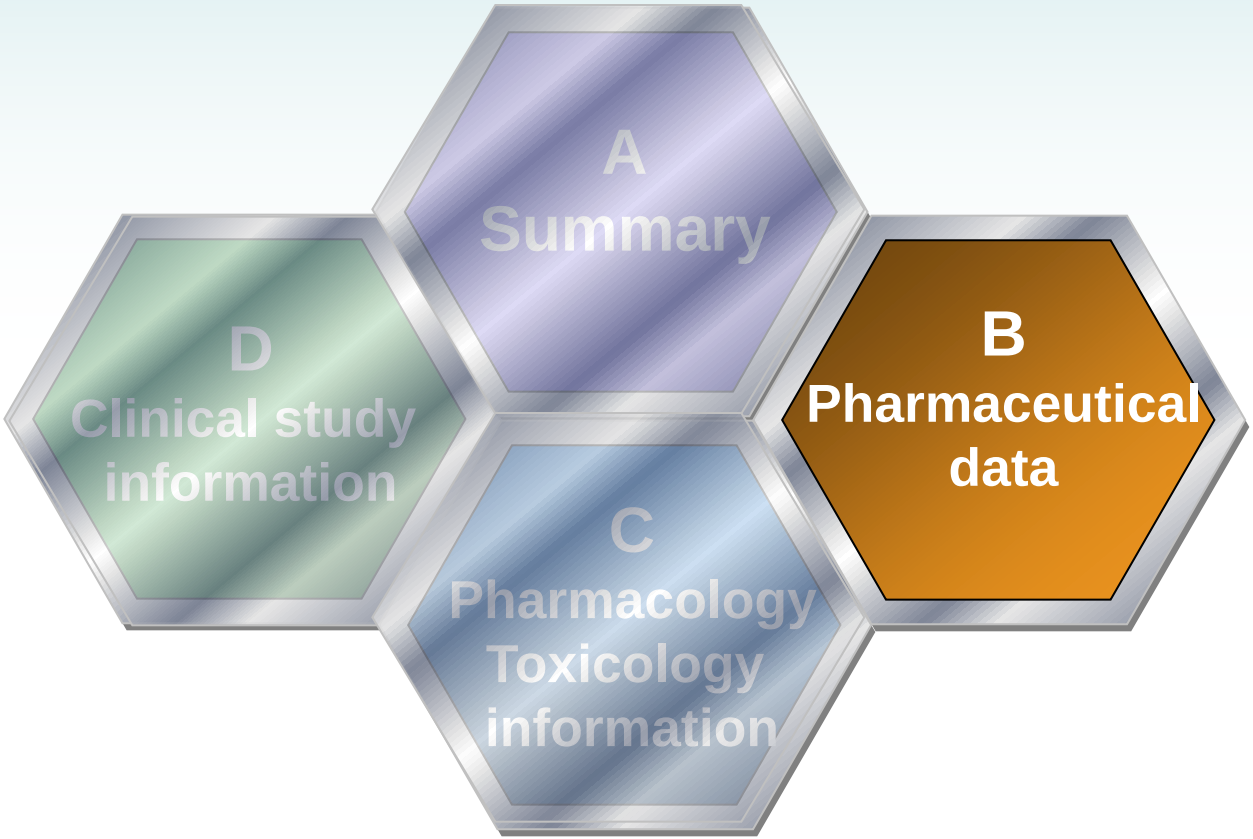
3) Objectives and basis for R&D

4) Summary of main study work

5) Draft of packaging insert, note to the draft, and latest literature

6) Design of packaging and labeling

4.B. Pharmaceutical data



No	Categories					
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8	+	*5	+	+	*5	*5
9	+	+	+	+	+	+
10	+	+	+	+	+	+
11	+	+	+	+	+	+
12	+	+	+	+	+	+
13	+	+	+	+	+	+
14	+	+	+	+	+	+
15	+	+	+	+	+	+

4.B. Pharmaceutical data

7) Summary of Pharmaceutical Study

8) Research information and relevant literature of the Production process of the drug substance, research information and relevant literature of formula and process of the preparations.

- **Formula**
- **Manufacturing process**
- **Manufacturing flow chart**
- **Screening process of formula**
- **Validation of manufacturing process**
- **Function of the excipients**
- **Selection basis of immediate packing material and container**

4.B. Pharmaceutical data

9) Study information and relevant literature for the chemical structure and components determination.

- **DMF**
- **Synthesis method, control of raw material and intermediate**
- **Specification of drug substance and intermediate**
- **Verification of structure of drug substance**

10) Study information and literature for quality specification.

- **Description**
- **Identification**
- **Validation (Assay method, related substances, microbial limit- EP, USP, CP)**
- **Quality comparison with original product**

4.B. Pharmaceutical data

11) Draft of quality specification and notes, and providing reference standard.

- **Draft of quality specification**
- **Reference standard**

12) Test report of drug sample.

- **CoA**
- **3 batches sample**

4.B. Pharmaceutical data

13) The source, test report and quality specification of drug substance and excipient.

- Excipients' spec and manufacturer
- Drug substance spec

14) Stability study and relevant literature.*

- Raw data
- Note: related substances should list data of all individual impurities and total impurities.

15) Selection basis and quality specification of immediate packing material and container.

*Stability study condition

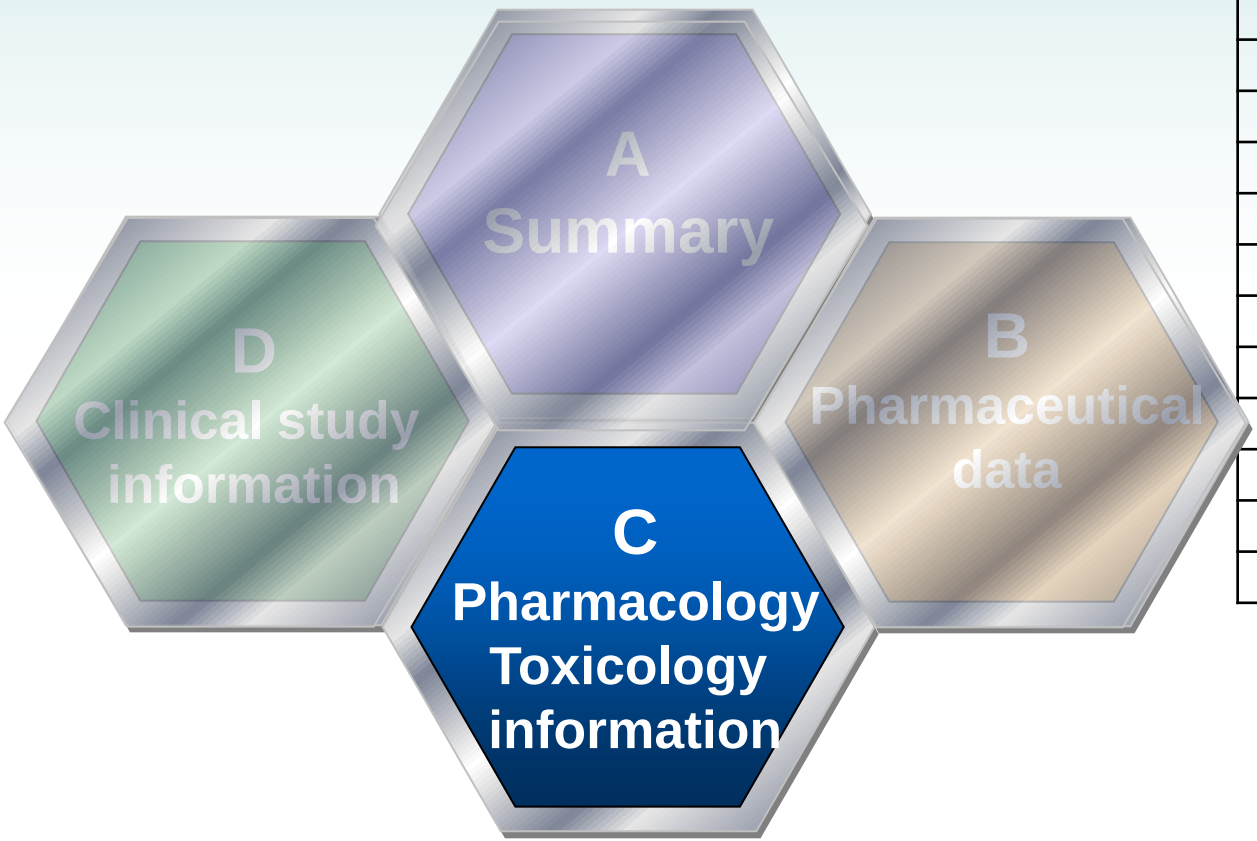
- **Stress Stability Study (1Batch)**

Condition	Storage	Minimum time period covered by data at submission
High temperature	60 ℃	10 days (0,5,10 D)
High humidity	25 ℃/ 90 ± 5 % RH	10 days (0,5,10 D)
Photo	4500 ± 500 Lux	10 days (0,5,10 D)

- **Accelerated/Long term Stability study (3 Batches)**

Condition	Storage	Minimum time period covered by data at submission
Accelerated	40 ± 2℃ / 75 ± 5 % RH	6months (0,1,2,3,6M)
Long term	25 ± 2℃ / 60± 5% RH	6 months (0,3,6M)

4.C Pharmacology Toxicology information



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21	*19	*19	*19	*19	*19	*19
22	*13	-	-	-	-	-
23	+	±	±	±	-	-
24	+	±	±	±	-	-
25	*8	-	*8	*8	-	-
26	*9	-	-	-	-	-
27	+	*20	*20	+	*20	-

4.C. Pharmacology and Toxicology study information

16) Summary of pharmacology and toxicology study.

17) Primary pharmacodynamics study and literature.

18) General Pharmacology study and literature.

19) Acute/single dose toxicity study and literature.

20) Repeated dose toxicity study and literature

4.C. Pharmacology and Toxicology study information

21) Special safety study and literature of hypersensitive (topical, systemic and photo-toxicity), hemolytic and topical irritative (blood vessel, skin, mucous membrane, and muscle) reaction related to topical and systemic use of the drugs.

22) Study and relevant literature on Pharmacodynamics, toxicity and pharmacokinetics change caused by the interactions amongst multiple components in the combination products.

4.C. Pharmacology and Toxicology study information

23) Study and literature of mutagenicity test.

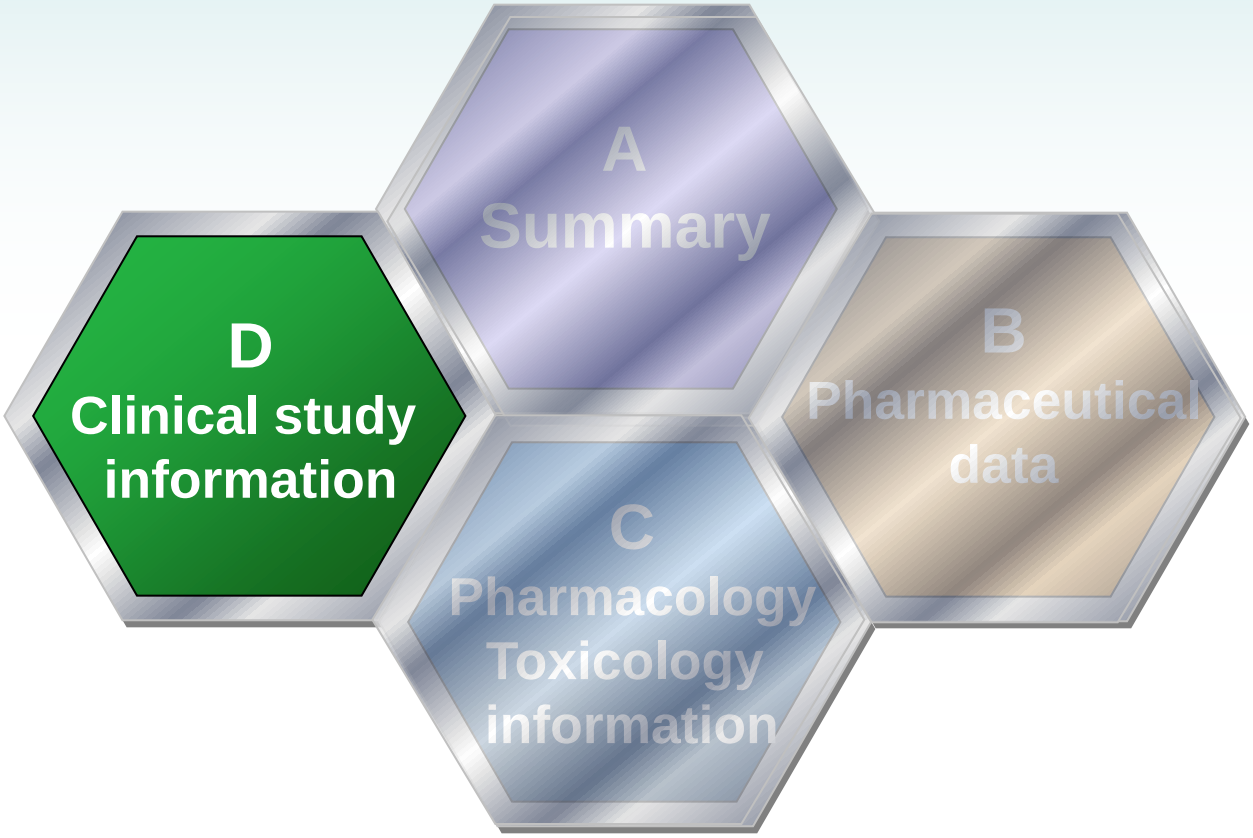
24) Study and literature of reproductive toxicity.

25) Study and literature of carcinogenicity test.

26) Study and literature of drug dependence.

27) Study and literature of pre-clinical pharmacokinetics.

4.D Clinical study information



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29	+	+	+	+	+	Δ
30	+	+	+	+	+	Δ
31	+	+	+	+	+	Δ

4.D. Clinical study information

28) **Summary of global clinical study information.**

29) **Clinical study protocol.**

30) **Investigator's Brochure.**

31) **Draft of Informed Consent Form, approval of the Ethics Committee.**

32) **Clinical study report.**

Table of application information item

Range	No	Registration Categories					
		1	2	3	4	5	6
A	1	+	+	+	+	+	+
	2	+	+	+	+	+	+
	3	+	+	+	+	+	+
	4	+	+	+	+	+	+
	5	+	+	+	+	+	+
	6	+	+	+	+	+	+
B	7	+	+	+	+	+	+
	8	+	*5	+	+	*5	*5
	9	+	+	+	+	+	+
	10	+	+	+	+	+	+
	11	+	+	+	+	+	+
	12	+	+	+	+	+	+
	13	+	+	+	+	+	+
	14	+	+	+	+	+	+
	15	+	+	+	+	+	+

Range	No	Registration Categories					
		1	2	3	4	5	6
C	16	+	+	+	+	+	+
	17	+	*16	±	*18	+	+
	18	+	*16	±	*18	+	+
	19	+	*16	±	*18	+	+
	20	+	*16	±	*18	+	+
	21	*19	*19	*19	*19	*19	*19
	22	*13	-	-	-	-	-
	23	+	±	±	±	-	-
	24	+	±	±	±	-	-
	25	*8	-	*8	*8	-	-
	26	*9	-	-	-	-	-
	27	+	*20	*20	+	*20	-
D	28	+	+	+	+	+	+
	29	+	+	+	+	+	Δ
	30	+	+	+	+	+	Δ
	31	+	+	+	+	+	Δ

+ Must be submitted *** According to the requirements** **- Information may be exempted**

Δ Denote that the provisions 4 **± Literature can be used instead of test information**

Thank You !