Drug Regulatory Requirement Overview in China

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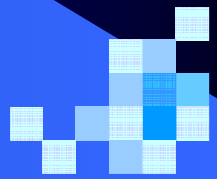
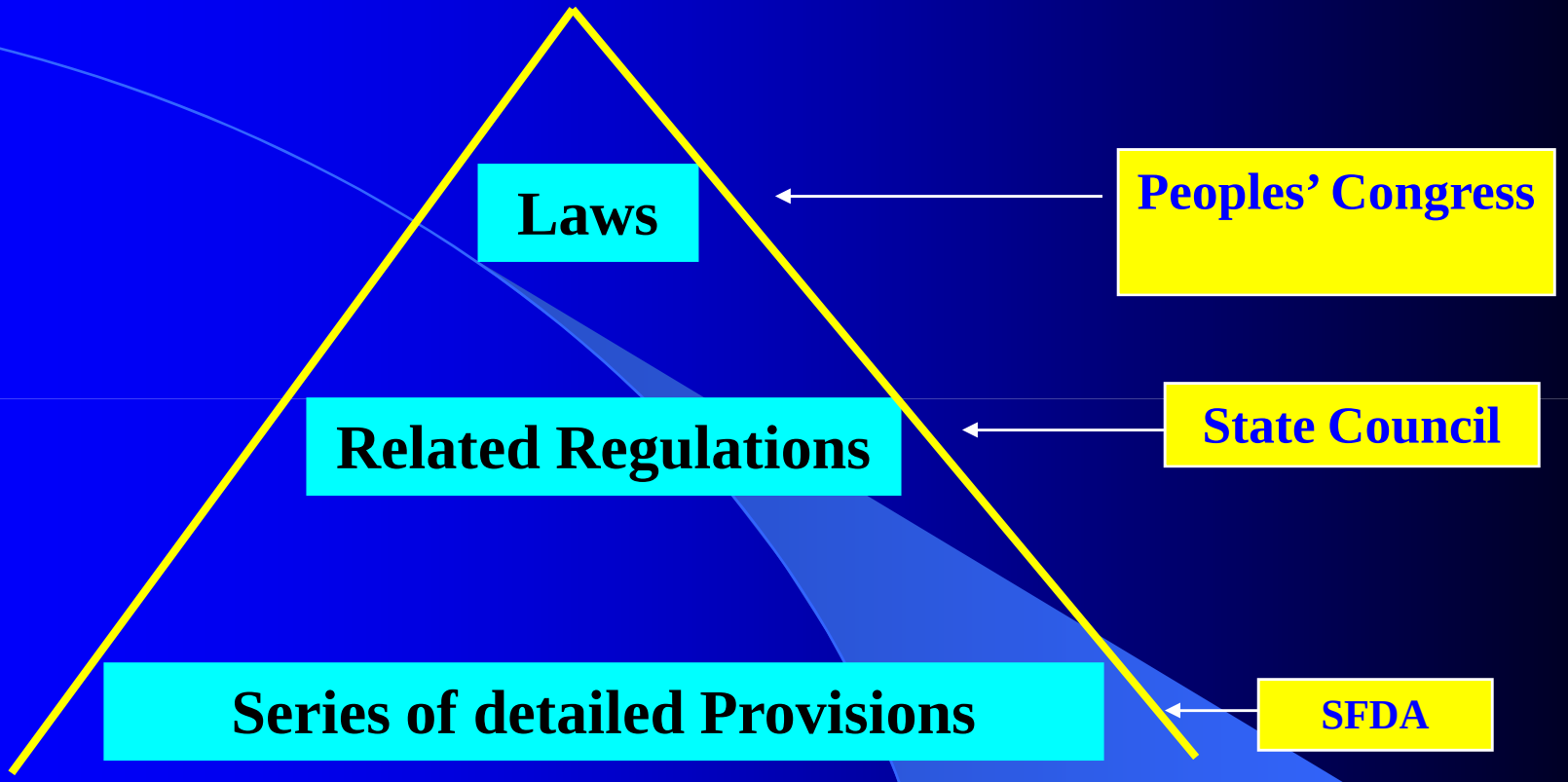
DEPARTMENT OF DRUG REGISTRATION
STATE FOOD & DRUG ADMINISTRATION

March. 2008, Bonn University



Three levels Regulatory system



Legislation

1. ***Drug Administration Law of P.R. China***
   (People's Congress, Amended, 2001.12.01)

2. ***Regulations for Implementation of the Drug Administration Law of P.R. China***
   (State Council, Amended, 2002.09.15)

3. ***Provisions for Drug Registration***
   (SFDA, Amended, 2007.10.01)

Law Requirements for Drug Registration

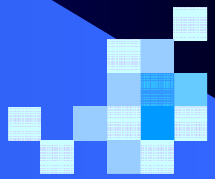
1. **the manufacturing of new drug or generics must be approved by SFDA, and a drug approval number shall be issued (all drugs have to be approved)**

2. **Drug importation must be approved by SFDA, while its quality, safety, and efficacy having been confirmed, and the *Import Drug License* shall be issued. The import drug shall be approved by the manufacturing country originally.**

3. **SFDA shall evaluate new drug application by organizing experts in the field, such as pharmaceutical, medical.**

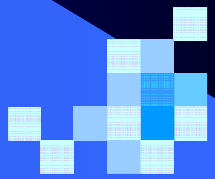
Legislation History Briefing

1. ***Provisions for New Drug Approval***
   (1985.07.01, Pharmaceutical, TCM)
2. ***Provisions for New Bio-Product Approval***
   (1985.07.01)
3. ***Provisions for Import Drug Administration***
   (1990.11.02, Pharmaceutical, TCM, Bio-Product)
4. ***Directives for New Drug Protection and Technology Transfer*** **(1987.03.24)**
5. ***Directives for the Approval of Foreign Sponsored Clinical Trials Tending to be Conducted in China***
   (1988.02.02)

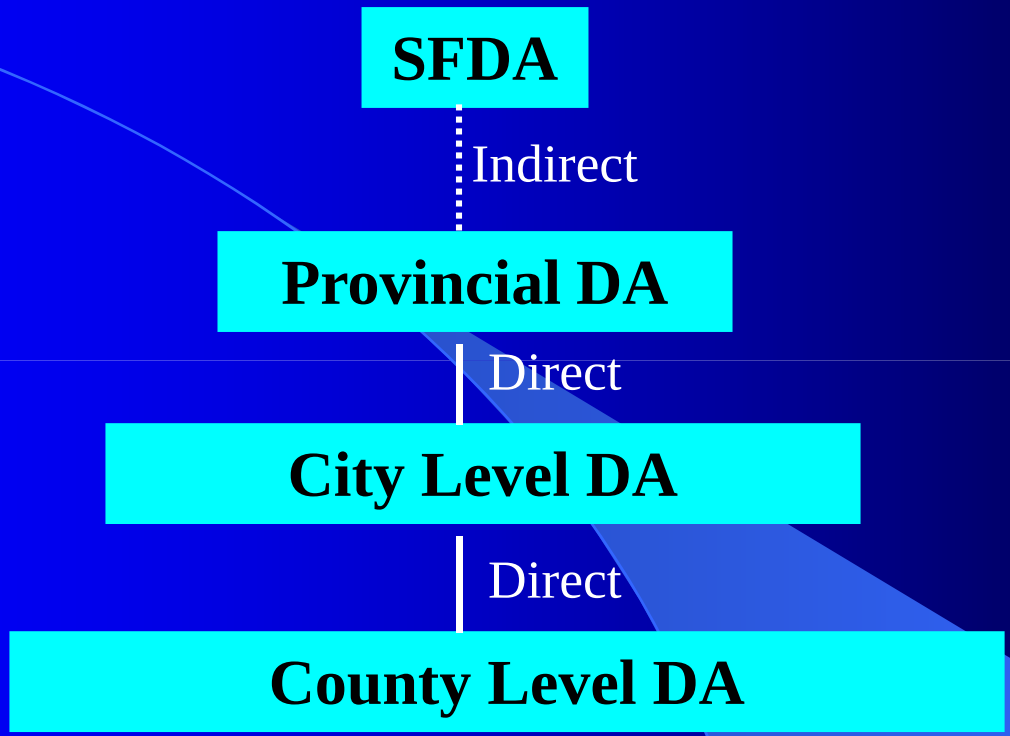


Legislation History Briefing

1. ***Provisions for New Drug Approval***
   (1999.05.01, Pharmaceutical, TCM)
2. ***Provisions for New Bio-Product Approval***
   (1999.05.01)
3. ***Provisions for Import Drug Administration***
   (1999.05.01, Pharmaceutical, TCM, Bio-Product)
4. ***Provisions for Generics Approval***
   (1999.05.01)
5. ***Directives for New Drug Protection and Technology Transfer***
   (1999.05.01)



Levels of Authority

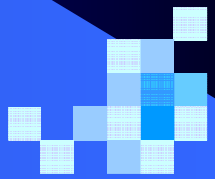


Responsible Organizations

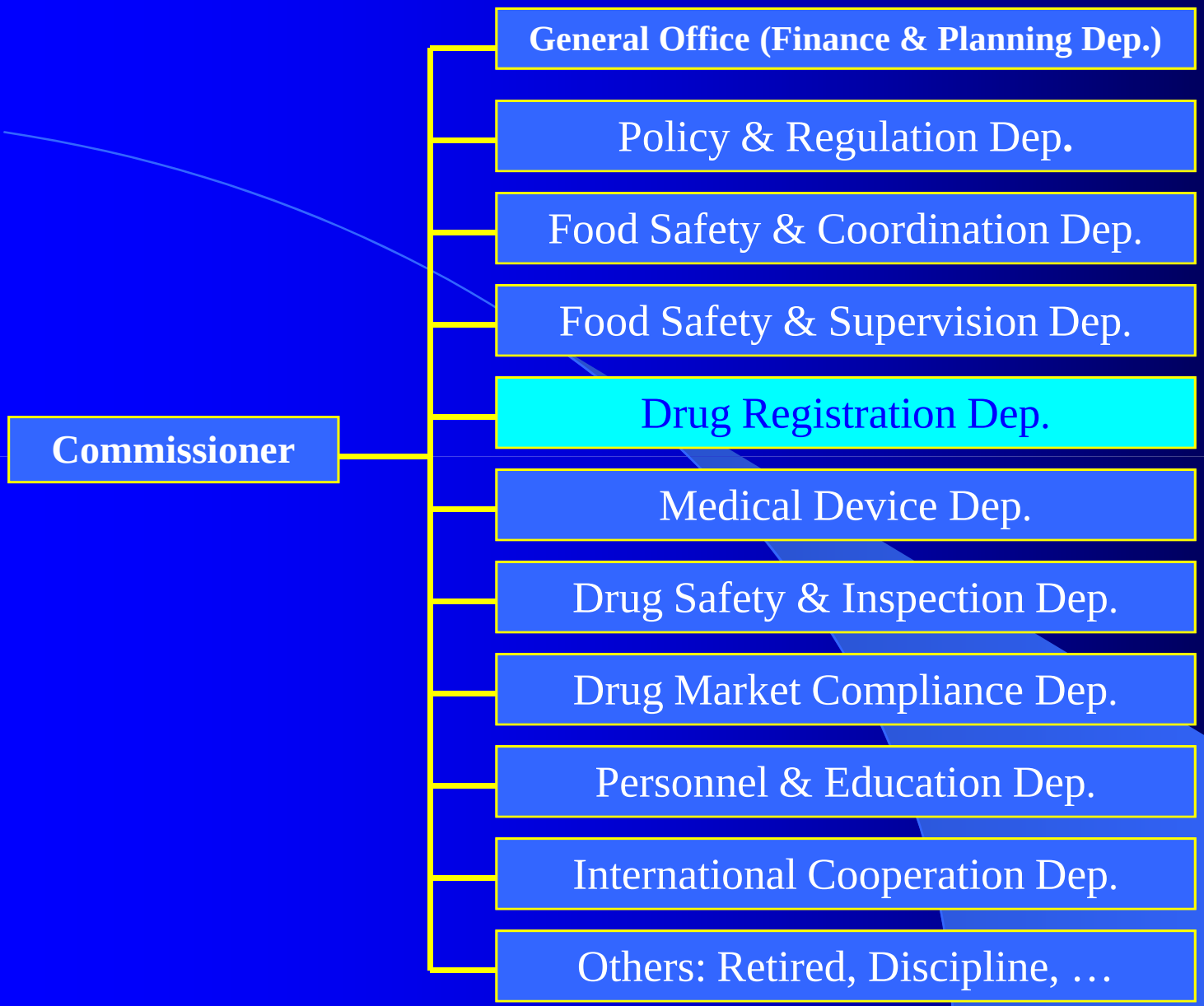
1. Department for Drug Registration of SFDA （DDR)
2. The Center for Drug Evaluation (CDE)
3. The National Institute for the Control of Pharmaceutical and Biological Products (NICPBP)
4. Chinese Pharmacopoeia Commission (ChPC)
5. Provincial authorities (Provincial DA) and quality control labs

Responsibilities Related to Registration

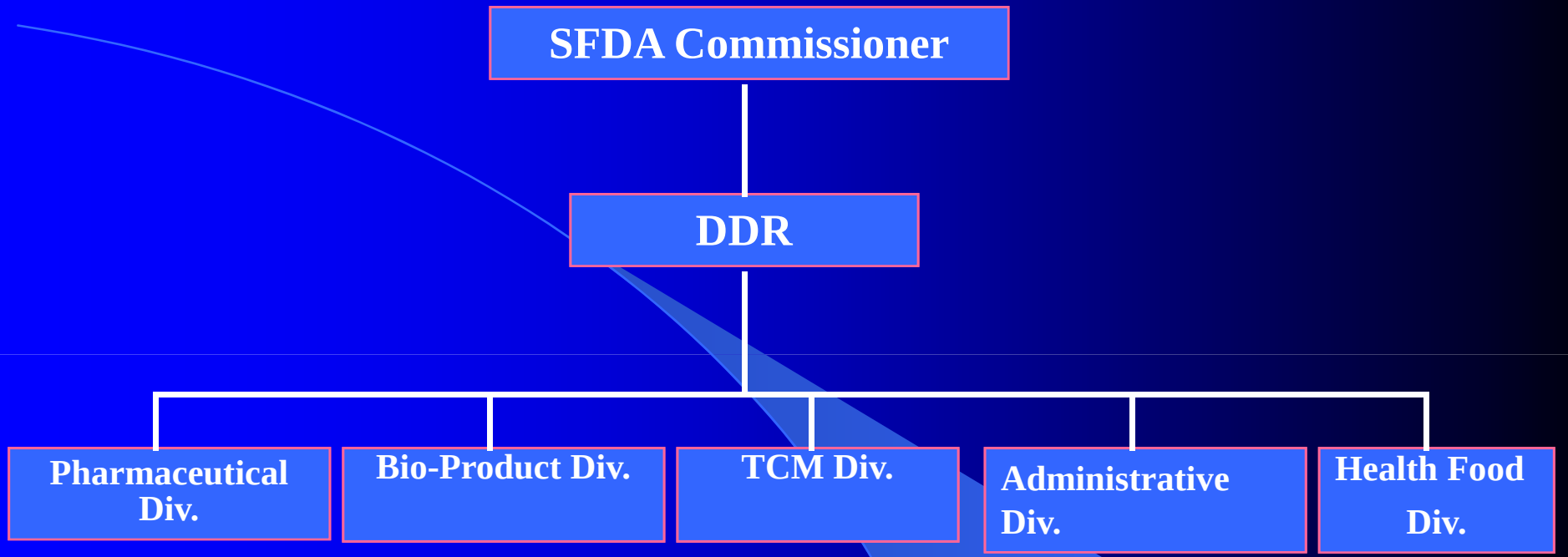
1. DDR
   - Policy maker regarding drug registration
   - Overall controlling drug registration functions around the country
   - Making decisions of final approval
2. CDE
   - Technical evaluation for all drugs
3. NICPBP
   - New drug specifications validation and verification
   - Reference substance preparation
4. ChPC
   - New drug temporary specifications to official specifications
5. Provincial DA
   - Site inspection
   - Primary review for the local applications
6. Provincial QC lab
   - Drug specifications validation and verification for the local applications



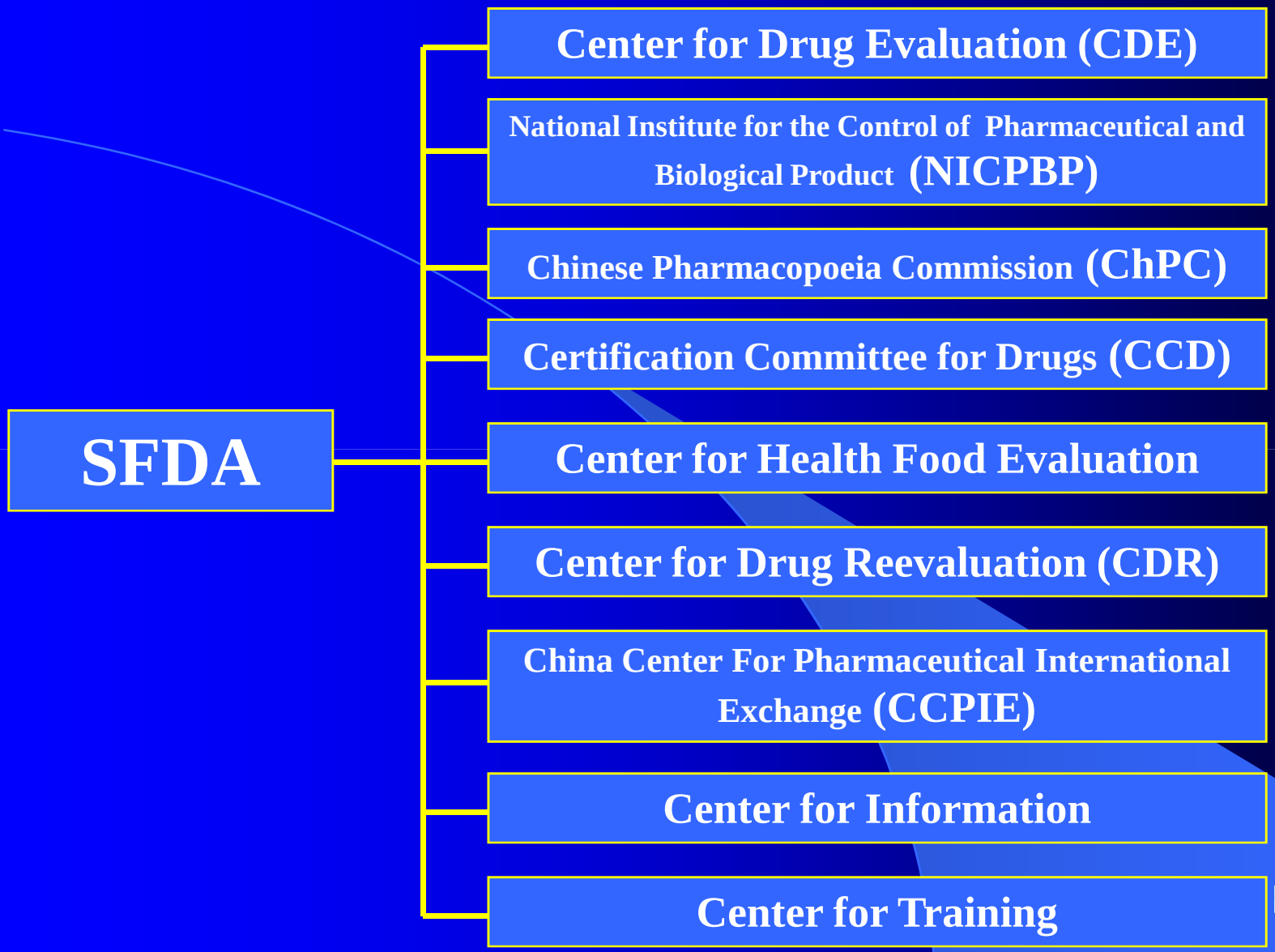
SFDA Organizational Chart



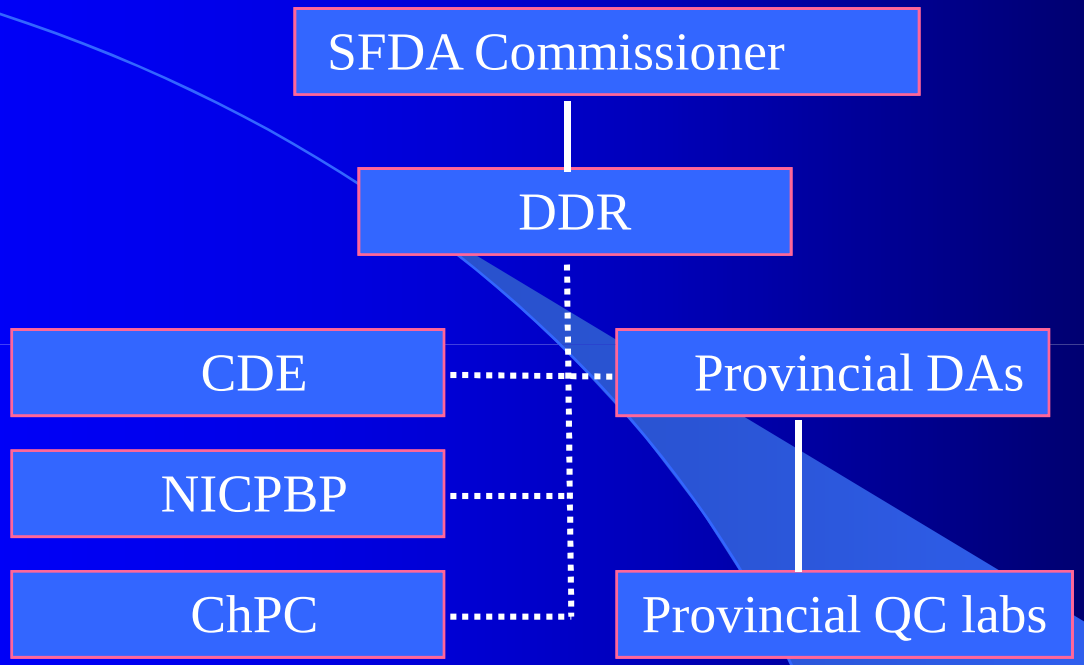
Department of Drug Registration



Affiliated Organizations to SFDA



Relationship of the organizations



Applicant Requirements

- Chinese nationality
- Domestic Law person: pharmaceutical company, organization, institute, not individual
- For Importation and multi-center international trial, applicant is foreigners, but, an Chinese representative has to be authorized, as the agent. The agent should be a law person

Application Dossiers

Part I: General data and Administrative Documents

Part II: Chemical, Pharmaceutical and Biological Data

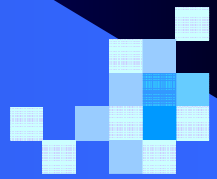
Part III: Pharmacological and Toxicological data

Part IV: Clinical Data

Application Dossiers(1)

PART I

1. Name of the drug
2. Document for attestation
3. Aim and justification of the selected project
4. Summary and review of the study results
5. Sample of package inserts, drafting description and reference materials
6. Sample of package and label



Application Dossiers(2)

PART II

7. Review of the pharmaceutical study.
8. Manufacturing process and literatures for API; the formulation, manufacturing process and literatures for pharmaceutical preparation.
9. Identification data and literatures for chemical structure or components,
10. Quality study data and literatures
11. Draft specifications, justification, and reference standards or reference substances.
12. Testing report of the drug sample.
13. The origin and specifications of the excipients.
14. Stability data and literatures
15. Immediate packaging materials selection, and its specifications

Application Dossiers(3)

PART III

16. Review of the pharmacological and toxicological study data.

17. The main pharmacodynamics data and literatures

18. General pharmacology data and literatures

19. Acute toxicity data and literatures.

20. Long term toxicity data and literatures

21. Special toxicity data and literatures related to topical and systematic administration, such as hypersensitivity (topical, systematic and photosensitive toxicity), hemolysis and topical (blood vessel, skin, membrane muscle, etc.) irritation, etc.

22. Interaction data and literatures of efficacy, toxicity and pharmacodynamics for multiple components.

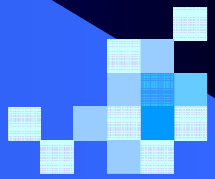
23. Mutagenicity data and literatures.

24. Reproductive toxicity data and literatures

25.Carcinogenicity data and literatures

26.Drug dependence data and literatures

27.Animal pharmacokynetics data and literatures



Application Dossiers(4)

PART IV

28.Overview of related clinical study literatures.

29. Clinical study protocol and plan.

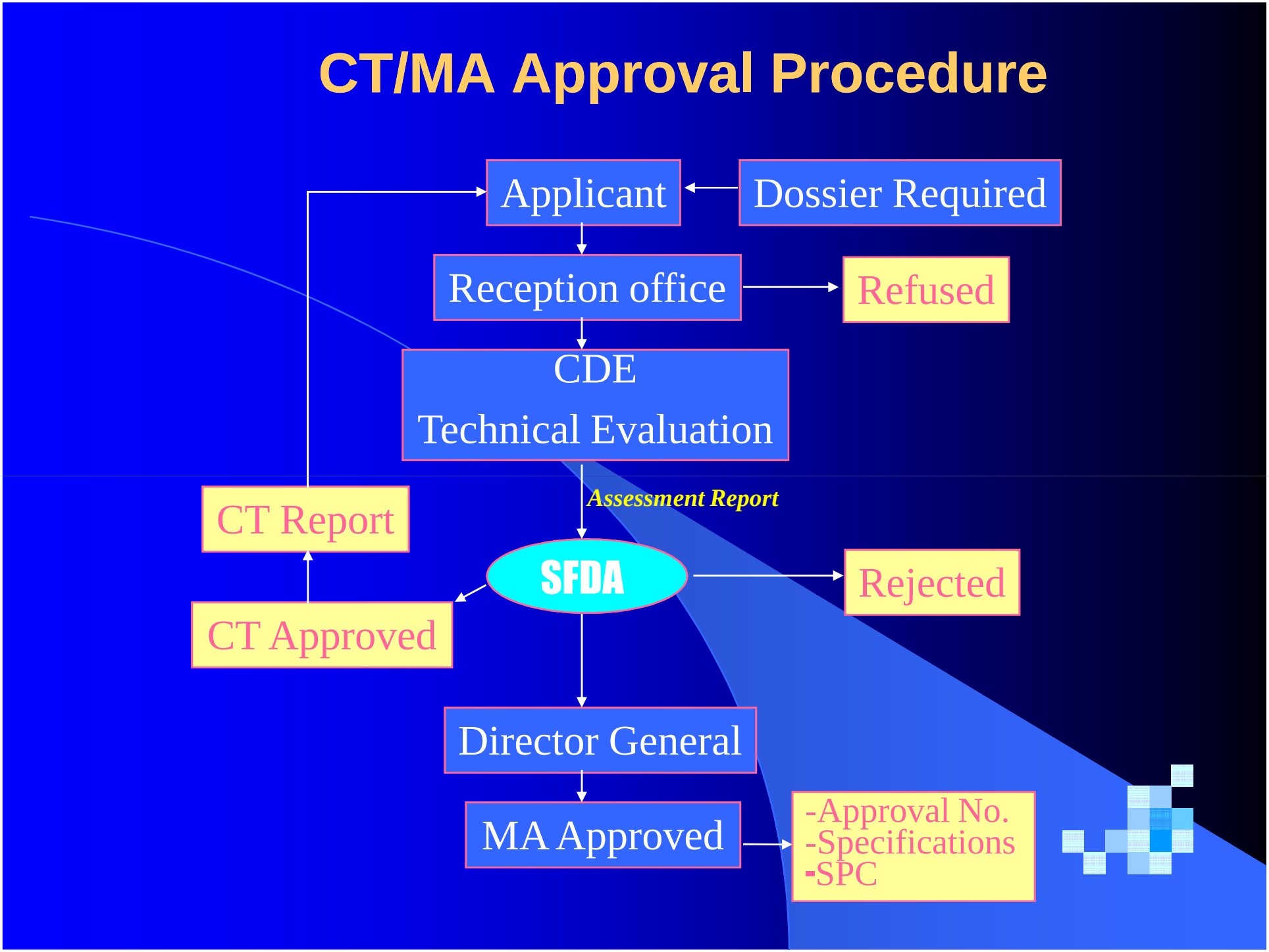
30. Clinical investigator Manual.

31. The copy of *Informed Consent* and ethics committee approval.

32. Clinical trial final Report.

Clinical Trial Approval Procedure

CT/MA Approval Procedure

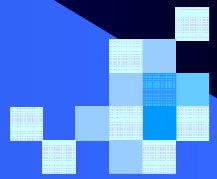


Technical Evaluation Concerns

1. Quality/Safety/Efficacy Aspects, based on self-produced dossier
2. Risk/Benefits Analysis
3. Literatures
4. Other Authorities approval information
5. Public health needs

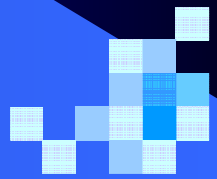
Evaluation and Approval Timelines

1. Provincial DA Primary Evaluation: 30 days
2. Provincial QC lab's tests:60 days; Bio-product: 90 days
3. SFDA Dossier Receiving: 5 days
4. CDE technical Evaluation for CTA: 90 days
   (Special Procedure: 80 days)
5. CDE technical Evaluation for new drug production application: 150 days (Special Procedure : 120 days)
6. CDE technical Evaluation for generics: 150 days
7. CDE technical Evaluation for variations: 40 days
8. SFDA marketing approval: 30 days
   (Special Procedure : 20 days)



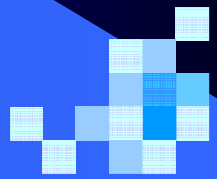
Special Procedure

1. TCM derived from Herbal, animal, and mineral that have never been previously used as therapeutics
2. New chemical entity (NCE)
3. Anti-HIV/AIDS products(treatment, prevention, Diagnosis)
4. Products for malignant tumor
5. Products for rare diseases (orphan drugs)
6. Products for the diseases that efficacious treatment are not available yet



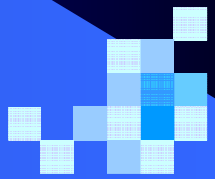
Registration Decisions

1. Approval
2. Approval with conditions
3. Rejection
4. Withdrawal



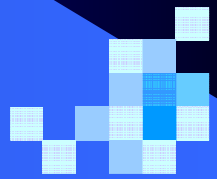
Registration Variations (1)

1. Applying Drug Approval Number with a already issued New Drug Certificate
2. Applying trade name
3. New indications
4. New strengths
5. Changes to excipient for an approved formulation
6. New manufacturing process
7. Specifications amending
8. Changing of drug validation
9. Changes of immediate materials
10. New drug technology transfer
11. Temporary specifications to official specifications
12. Changes of drug name, manufacturer name, registered address, package size, etc. , for import drug
13. New manufacturing site for import drug
14. New packager for import drug



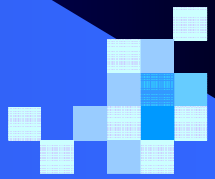
Registration Variations (2)

15. Repackaging in China
16. New suppliers of API for import drug
17. Name Changing of domestic manufacturer
18. New production site for domestic manufacturer
19. Changes to insert sheet according to SFDA requirements
20. Amending the safety part of insert sheet
21. Using of new label
22. New package size for domestic manufacturer
23. New suppliers of API for domestic manufacturer
24. Changes to the appearance of a finished product
25. New agent for import drug applications



Technical Guidelines

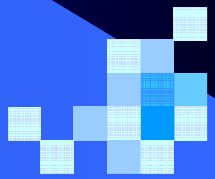
1. Chemical Structure Identification
2. API synthesis route
3. API Specifications
4. Chemical Product formulation and Manufacturing Process
5. Stability Study
6. Pre-clinical Toxicity Study
7. Single-Dose Toxicity Study
8. Repeated-Dose Toxicity Study
9. Pre-clinical PK Study
10. PK Study for Immediate Release, Sustained Release and Controlled Release Dosage Forms
11. Pre-clinical PK Study for New Bio-product
12. Clinical PK Study for Chemical Product
13. Human Bioavailability and Bioequivalence Study for Chemical Product
14. PK Study for New Bio-product
15. Bio-statistic for New Chemical Product and Bio-product
16. Chemical Product Pharmaceutical Study and Specifications
17. Clinical trials for TCM



Technical Guidelines

18. Active virus-vectored vaccine products for protective use
19. Pre-clinical trial of DNA vaccines for productive use
20. Clinical trial of AIDS vaccine
21. Quality control of DNA recombinant products for human use
22. Quality control of monoclonal antibody for human use
23. Study and quality control for human gene therapy use
24. Study and quality control for human somatic cell therapy use
25. Quality control of allergen
26. Manufacturing and quality control of bovine serum used for cell culture

Around 50 guidelines in total



Patient Number Requirements

For NCE

1. Statistically meaningful
2. The minimum patient number requirements:
   - Phase I: 20-30 patients
   - Phase II: 100 patients
   - Phase III: 300 patients
   - Phase IV: 2000 patients

For first importation application:

1. PK study
2. 100 pairs of patients , controlled, randomized, study
3. At least 60 patients for each indication

Control of CT Samples

- Manufactured in GMP facilities
- Adequate scale-up
- Freely provided to subjects
- Sales not allowed
- “ For Clinical Trial Only” must be placed on the label

International Clinical Trial Pre-conditions

- **Drug already marketed abroad, or at least Phase II trial or Phase III trial has already commenced abroad**

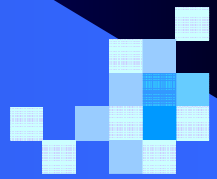
- **No any trials for vaccines without marketing authorization abroad**

International Multi-center Trial Result Use

- For drug importation application, after the marketing approval by original countries or regions
- For domestic manufacturing application
- For ICH region marketing application

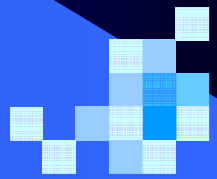
Rules for International Multi-Center Trial

- Phase I study repeated among Chinese population for some trials
- Report all adverse event of the whole trial, not only those found in China
- Inform SFDA of the ending of a trial, by preparing a Clinical Trial Report
- Only way to utilize the result is by submitting the whole set of data from the whole multi-center trials



Prospected Benefits from International CT

- Learn more international experiences
- Better GCP compliance by rigid monitoring, auditing and inspection
- More qualified investigator through the training and practice of international trials
- Less money required from government budget for GCP training, and more objectives can be achieved
- Possibly early access to new products, beneficial to public health

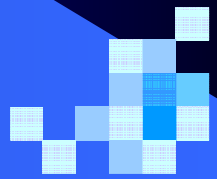


Characteristics of Chinese CT System

- Clinical Trials must be approved by SFDA prior to ethics committee approval
- Trials must be conducted by designated hospitals
- Designated hospitals are pre-selected and accredited by SFDA and MOH, as Clinical Bases
- Good Clinical Practice (GCP) works as guideline
- Large part trials for Generics

China GCP

- Published in 1998, amended in 1999, latest reversion Aug. 6, 2003
- Protecting subjects is the utmost purpose (such as Informed Consent)
- Helsinki Declaration as fundamental
- ICH, WHO guidelines as bases



CGCP –ICH GCP Comparison (1)

- The principals and must parts of CGCP are the same with ICH GCP
- Some parts of CGCP are stipulated and enforced by China Pharmaceutical Law by National People's Congress, The Implementation Regulation of Pharmaceutical by State Council, the Provisions for Drug Registration by SFDA
- CGCP published by SFDA as regulation, with more legal enforcement and obligation requirements; ICH GCP is more voluntarily intended.
- Some parts of CGCP are less in details due to its legal orientation. But with many supplementary official explanation, notification for each detailed issue in conforms with ICH GCP

CGCP –ICH GCP Comparison (2)

- **Medical institutions are pre-qualified and pre-approved by MOH and SFDA according to the Law. A List of Clinical Trial Medical Institutions is established. 251 Institutions in the List**
- **Any clinical trial shall be conducted by Investigators from among medical institution in the List only.**
- **Any trial with the participation of medical institution not in the list, shall be approved by SFDA in advance at case by case bases**
- **Amendment of protocol up to IRB/IEC approval, and with a notification to SFDA afterwards**

CGCP - ICH GCP Differences

- A clinical trial has to be approved and a Certificate of Clinical Trial Approval issued by SFDA, prior to IRB/IEC approval.
- An application for clinical trial approval with strict CMC part requirement
- The establishment of IRB/IEC is required to notify SFDA
- IRB/IEC shall be male and female balanced in proportion
- Record shall be kept for 5 years, ICH is 3 years
- For Bio-product, the investigational products must be tested before its supplying, by SFDA designated official Quality Control Institute

Challenges

- GCP is relatively a new area, investigators lack of experiences
- China regulatory system currently without IND and NDA differentiation in technical dossier, procedure, and timing. Causes delay for clinical trial application
- EC is separately established by each hospitals involving a trial
- Lack of social supportive policy is a bottle-neck for better GCP implementation, such as insurance.

Registration Appeal Policy

1. Only for rejections
2. Made within 60 days from the time the rejection received, directly to DDR
3. Only for the original application purpose
4. No additional data can be submitted, other than that already in SFDA
5. SDFA should make a decision within 50 days
6. Applicants can make a further *Administration Appeal* following another procedure settled down by *Provisions for Administration Appeal*

Patent and Undisclosed Date Protection

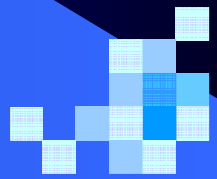
1. Any application must not infringe the patent concerned.
2. Applicant shall submit a announcement letter promising that specific application did not infringe any patent
3. Undisclosed data of NCEs shall be protected for a 6-year period since the day of approval
4. No any staffs and personnel related to evaluation and approval could disclose any confidential information of any application

Policy Making Mechanism

- Ultimate purpose to protect public interest, especially the patients
- As much as possible to take public opinions in policy making
- Regulation drafts put on SFDA web site always
- Meetings hold with interests parties (applicant, manufacturer, experts, associations, researchers, etc.)

Transparency and Openness

- Experts meeting announced in advance
- Applicant invited to evaluation meeting, direct dialogue with evaluators
- Evaluation and approval procedure of main steps traceable to every applicant by entering application number to SFDA web-site
- Each Tuesday. Official face-to-face consultation with questions raised by applicant at SFDA facilities.
- All drug list available on SFDA web site upon its approving



Principles of Policy Improvement

- New situations: Social, Economical, Political
- Changed statutory conditions: Licensing Law of PR China
- WTO promises: Undisclosed Data
- International common practices: WHO guidelines, ICH guidelines
- Benchmarks: other authorities

Some Recent Moves

- The new Provisions for Drug Registration is implemented in Oct. 1, 2007 in China
- CTD format of application package can be used first time for China, despite the administrative part
- Must of the test requirement for investigational products are dismissed since Oct. 1
- China regulatory system became more open and transparent , with more international communications, cooperation
- International common practices plays a very important role for the improvement of CGCP

Areas of Future Development

- **Differentiation between IND and NDA: currently the same in all contexts**
- **Differentiation between Technical Dossier for IND and NDA**
- **Differentiation between approaches to technical evaluation for IND and NDA : now full evaluation**
- **Reduction of the time required for CT evaluation and approval**
- **Supports of more international multi-center CT for all the phases**

THANK YOU

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