SFDA 's Perspective of Medical Review for Drug Registration

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Outline of Presentation

- ***Statutory and Technical Requirements for Drug Registration***
- ***Trend of Applications Submitted to SFDA***
- ***Review Strategies on Different Applications***
- ***Communication & Cooperation***

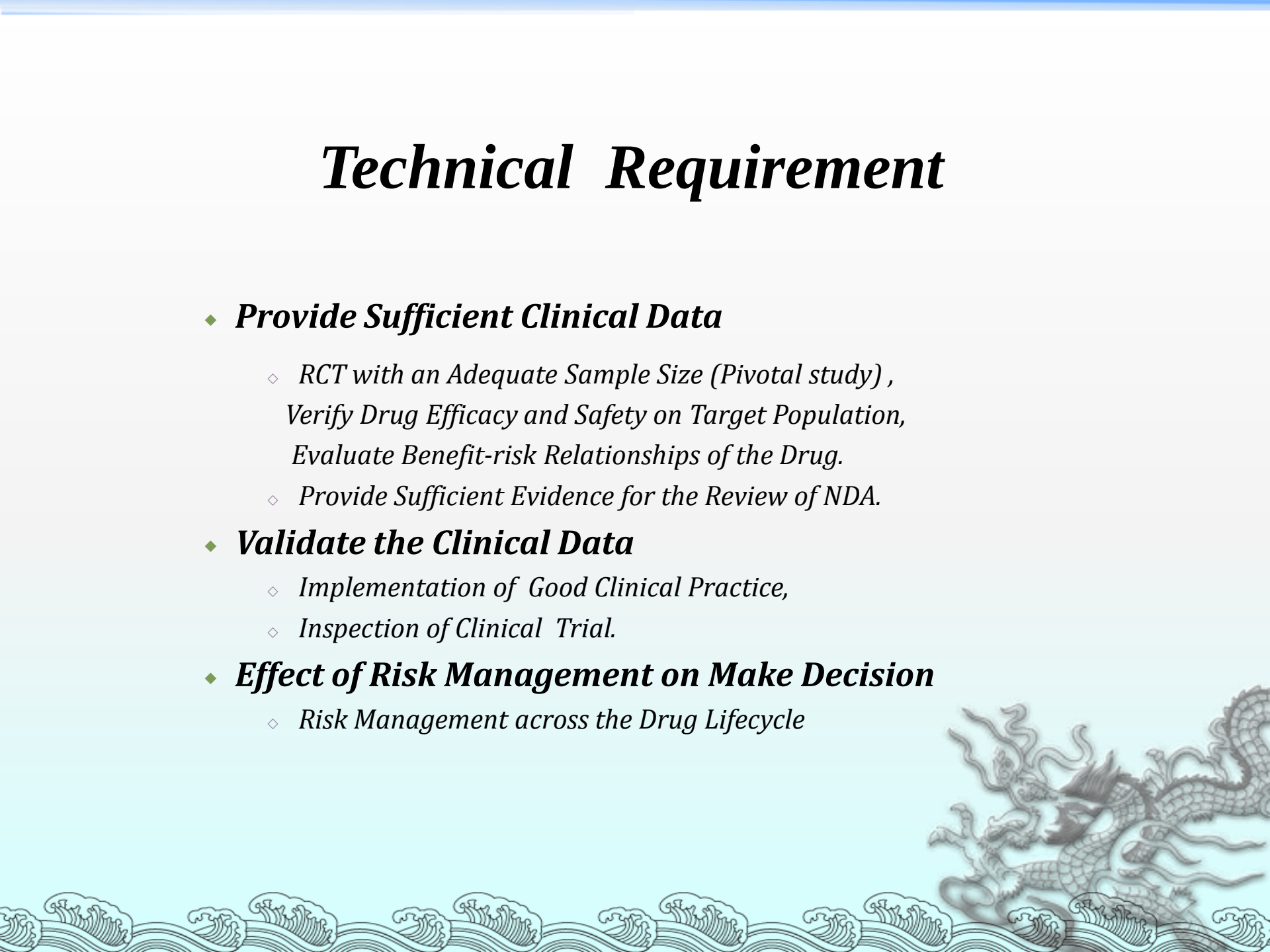
1. Statutory and Requirement for Drug Registration

Statutory Requirements

- ***Drug Administration Law (2001)***
- ***Regulations for Implementation of the Drug Administration Law(2002)***
- ***Provisions for Drug Registration(2007)***
  - *Clinical trials shall be conducted for NDA applications.*
  - *A clinical trial consists of phases I, II, III and IV.*
  - *The study (Phase III) shall be a randomized blind controlled trial with an adequate sample size.*

Technical Requirement

- ***Provide Sufficient Clinical Data***
  - *RCT with an Adequate Sample Size (Pivotal study) , Verify Drug Efficacy and Safety on Target Population, Evaluate Benefit-risk Relationships of the Drug.*
  - *Provide Sufficient Evidence for the Review of NDA.*
- ***Validate the Clinical Data***
  - *Implementation of Good Clinical Practice,*
  - *Inspection of Clinical Trial.*
- ***Effect of Risk Management on Make Decision***
  - *Risk Management across the Drug Lifecycle*

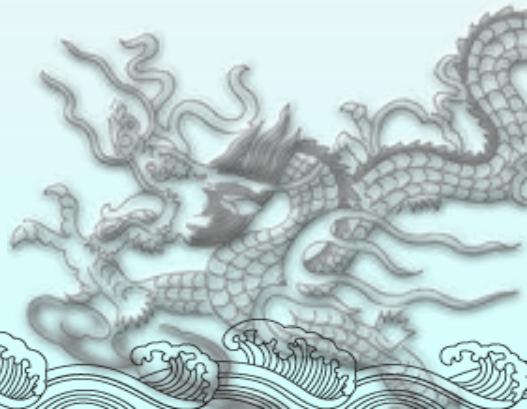


Stakeholders

- ***Sponsors***
  - *Submission IND application to agency for regulatory authority approval*
  - *Confirmation of review by ethics committees*
  - *Provision with information and training necessary*
  - *Monitoring clinical trial*
- ***Independent Ethics Committee***
  - *Responsibilities : Ethics, law, science, Part of Risk Management*
  - *The ethical review & regulatory review,*
  - *Responsibilities of the Ethical Committee Need Improvement.*

Stakeholders

- ***Principle investigator***
  - *Responsibilities*
    - *Protection of the right, safety and well-being of human being*
    - *Communication with IRB/IEC*
    - *Informed Consent of Trial Subjects*
    - *Compliance with Protocol*
    - *Review the report of adverse events*
  - *Need Improvement*
- ***Other factors***
  - *Regulatory environments*
  - *Other factors , for example ,subject ,IDMC, insurance, etc.*

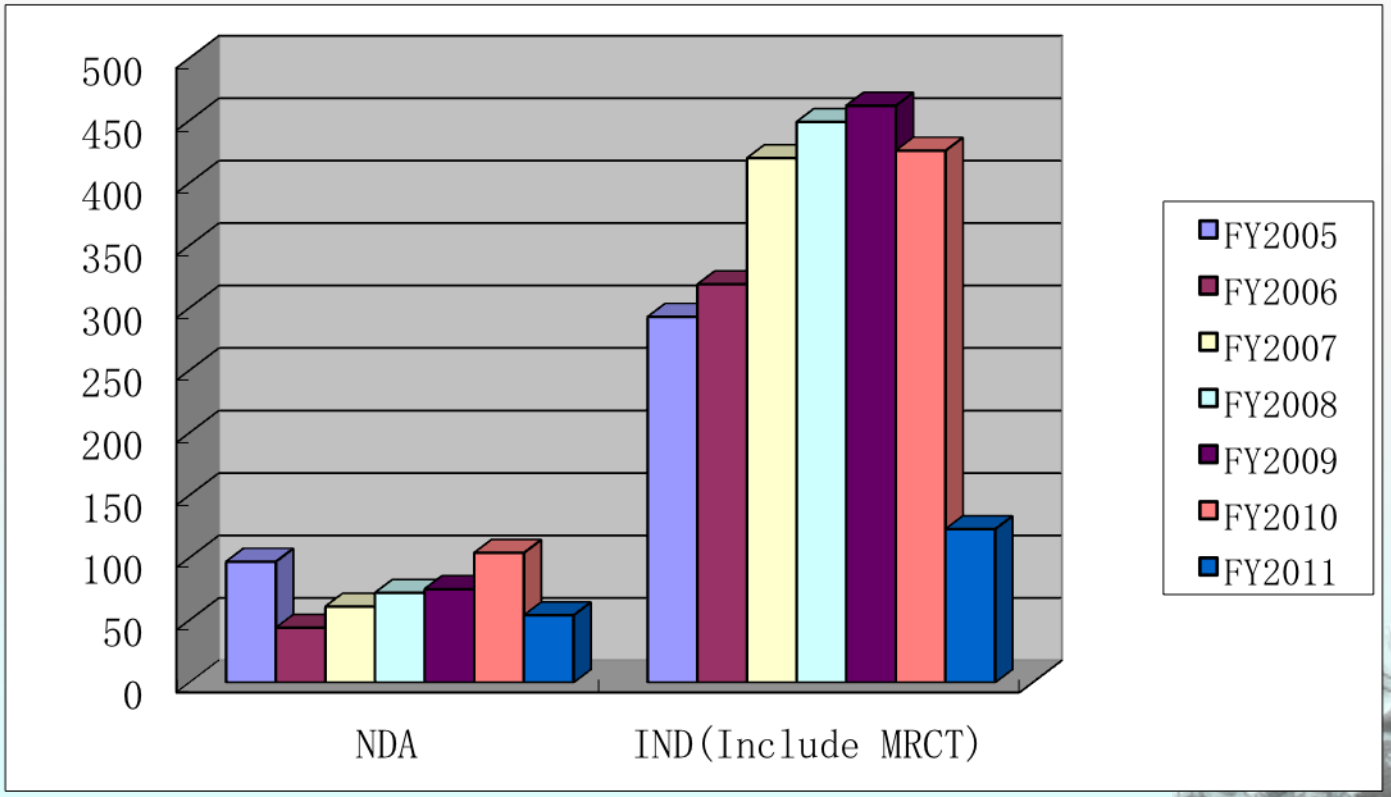


2. Trend of Applications Submitted to SFDA

6 Decision-making Track

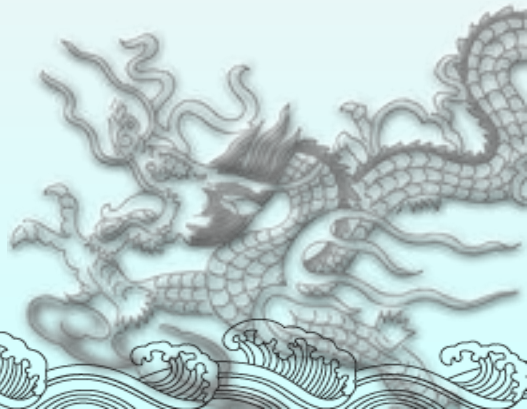
- *According Review Task Management Principles and Practices*
  - *IND(Investigational New drug）Applications*
  - *NDA(New Drug Application）Applications*
  - *ANDA(Abbreviated New Drug Application) Applications*
  - *Conceptual - bridging New Drug Applications*
  - *Supplementary Applications*
  - *Re-registration Applications*

Numbers of IND and NDA submitted to SFDA (2005.1-2011.6)



Trend of Applications Submitted

- *IND application ↑*
  - *Most of them are Conceptual New Drug Applications*
  - *NCE or NME ↑*
  - *MRCT(Multiple randomization control trials) ↑*
  - *Regional MRCT ↑*
- *NDA application ↑*
  - *Most of them are Conceptual New Drug Applications*
  - *NCE or NME ↑*
  - *Using MRCT data for registration ↑*



3. Review Strategies on Different Applications

Review strategy

- *Review under Laws and Procedures*
  - *SFDA: Special review and approval procedure for drug registration of the state food and drug administration(2005.11.18)*
  - *CDE: Principles and procedure of scientific and technological review for drug registration(2011.3.23)*
- *Review according Scientific rules*
  - *Investigational New drug Applications Review*
  - *Conceptual - bridging New Drug Applications Review*
  - *New Drug Applications Review*
  - *Multiple randomization control trials Applications Review*

Review strategy

- *Review under Laws and Procedures*
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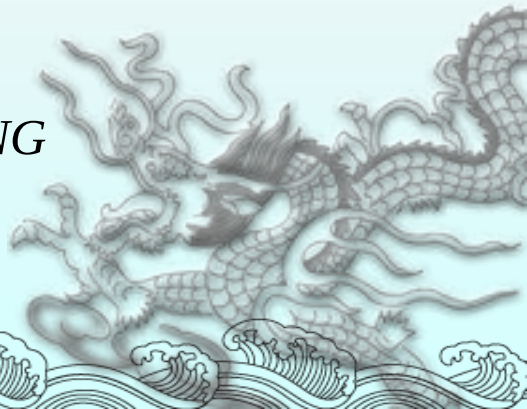
IND application

- *The IND application contain information in three broad areas:*
  - *Clinical Protocols and Investigator Information*
  - *Animal Pharmacology and Toxicology Studies*
  - *Manufacturing Information*
- *Clinical Review Based on Protocol Design and Data:*
  - *Science of Clinical Protocols*
  - *Safety of Research Subjects*
    - *to known and potential safety risk, make risk management plan.*
    - *To serious safety risk, Independent Data Monitoring Committee involve*
- *Communications :*
  - *pre-IND , END-OF-PHASE 2 , PRE-NDA MEETING*
  - *Advisory Committees meeting*



NDA Applications

- *Efficacy*
  - *Review the Randomization Control Clinical Trial submitted*
  - *Confirm the Efficacy of the Investigational Drug*
- *Safety*
  - *overall known and potential risks ,from nonclinical study, clinical trial, literature, postmarked report, etc.*
- *Make Pharmacoviligance plan & risk management plan*
- *Risk benefit assessment(BRA)*
  - *BRA is the "heart" of determining the value of the of product .*
  - *Balance risk and benefit of the product in target indication population.*
  - *making more objective, transparent, and evidenced-based decisions.*

Review of MRCT Application

Article 44 An overseas applicant intending to conduct an IMRCT in China shall submit an application to the SFDA in accordance with the Provisions, and fulfill the following requirements:

(1) the drugs used for clinical trials shall be already approved ,or in phase II or III clinical trial overseas.

(2) while approving to conduct an IMRCT, the SFDA may require the applicant to conduct phase I clinical trial first in China;

(3) when conducting an IMRCT in China, if there are any observed serious adverse reaction and unexpected adverse reaction associated with the drug in any country, the applicant shall report to the SFDA in time;

(4) the applicant shall submit a complete clinical trial report to the SFDA after the completion of a clinical trial; and

(5) the data obtained from an IMRCT for drug registration application in China shall be in conformity with the requirements on clinical trial in the Provisions. All the study materials of the IMRCT shall be submitted.

Review of MRCT Application

Medical review based on

- *protocol & data*
- *Target indication population*

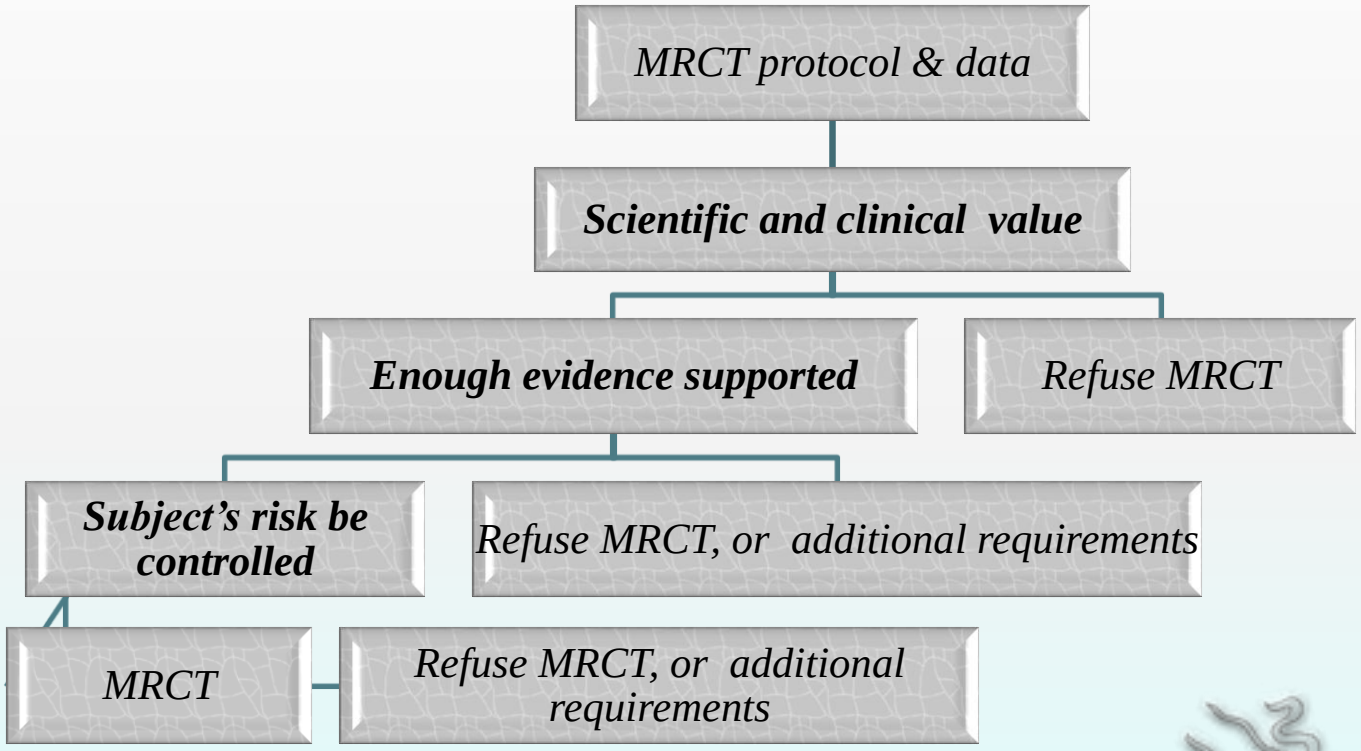
Content of Assessment

- *Science of Clinical Protocols*
- *Safety of Research Subjects*

Questions based review

- *Are there scientific and clinical value of investigational drug?*
- *Are there the evidence for clinical trial supported ?*
- *Can safety risk of Research Subjects be controlled?*

Figure 1. Review Procedure of MRCT



Review MRCT Data for Drug Registration

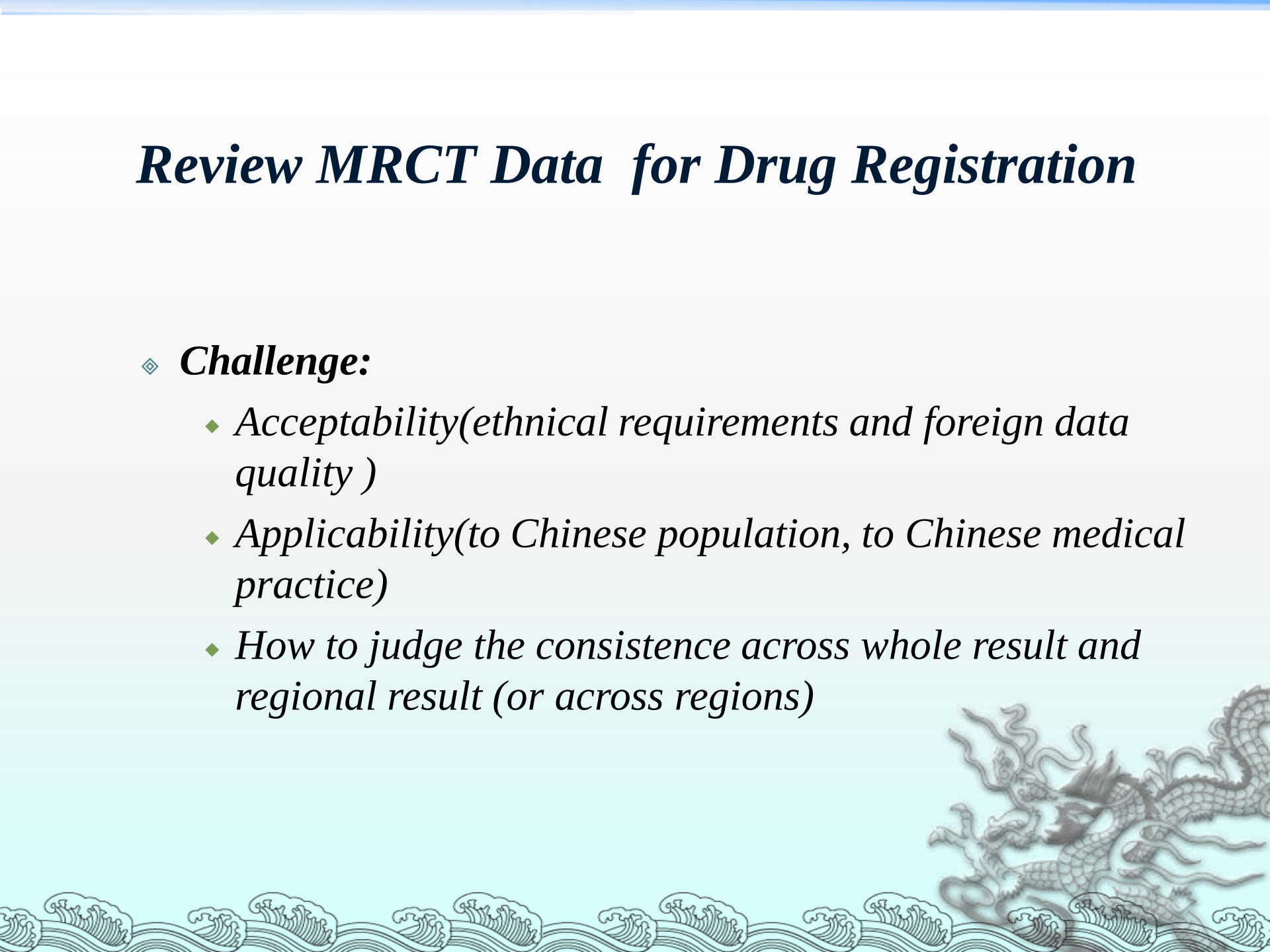
- ***Assessment of Complete Clinical Data Package***
  - ***Efficacy and safety in study population and target labeling population***
  - ***MRCT involved Chinese patients (Pivotal Study?)***
- ***Consistence between regional patients and overall patients***
  - *If all data meets the statutory and technological requirements, the product may be approved.*
  - *If not, another study with large sample size may be conducted.*
- ***No consistence between regional patients and overall patients***
  - *bridging study or clinical trial should be conducted.*

Review MRCT Data for Drug Registration

- ***Hierarchy of Persuasiveness:***
  - *Demonstration of effect in the entire study with statistically significant result in each region.*
  - *Demonstration of effect in the entire study, but non-significant effect in region of interest. Supportive data includes:*
    - *Consistent trends in endpoints across regions*
    - *Similar dose-response relationships across regions*

Review MRCT Data for Drug Registration

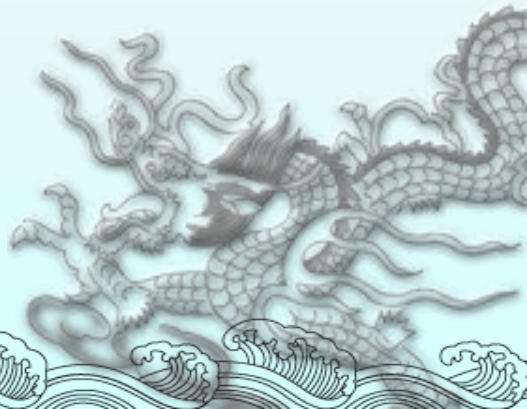
- ***Challenge:***
  - *Acceptability(ethnical requirements and foreign data quality)*
  - *Applicability(to Chinese population, to Chinese medical practice)*
  - *How to judge the consistence across whole result and regional result (or across regions)*



4. Communication & Cooperation

Communication & Cooperation

- *Communication and Cooperation:*
  - *Data management*
  - *Adverse events exchange*
  - *Risk managements*
  - *Ethical Issues*
  - *Regional cooperation*
  - *…*



Thank you for your attention!