New CFDA Requirements and its Implementation

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Disclaimer

- All information provided in this slides is provided for information purposes only
- Views expressed in this presentation are those of the speaker and not necessarily of Novartis

Biography

- Yi (Eason) Yang joined Novartis in 2010 and is currently Senior Principal Programmer

CFDA or CNDA

2013.03 – 2018.03

China
Food and
Drug
Administration

2018.03 – Present

China
National
Drug
Administration

Agenda

- CNDA Reform
- New Guidance & Guidelines
- Entresto™ CNDA Submission Case Study
- Summary

CNDA Reform

Regulatory Environment Before Reform

Challenging

- Lengthy and unpredictable review timeline
- Additional regulatory requirements
- Unclear technical requirements
- CDE resource issue
- Lack of connection among different authorities bodies

Inconsistent with global standards

- Local standards
- Local clinical data
- Local quality testing during CTA and NDA
- More CMC data
- Overseas marketing requirements

CNDA Reform

China State Council approved "Opinions on **Reforming** the Evaluation and Approval System for Drugs and Medical Devices" and was formally announced to the public on **August 9, 2015**

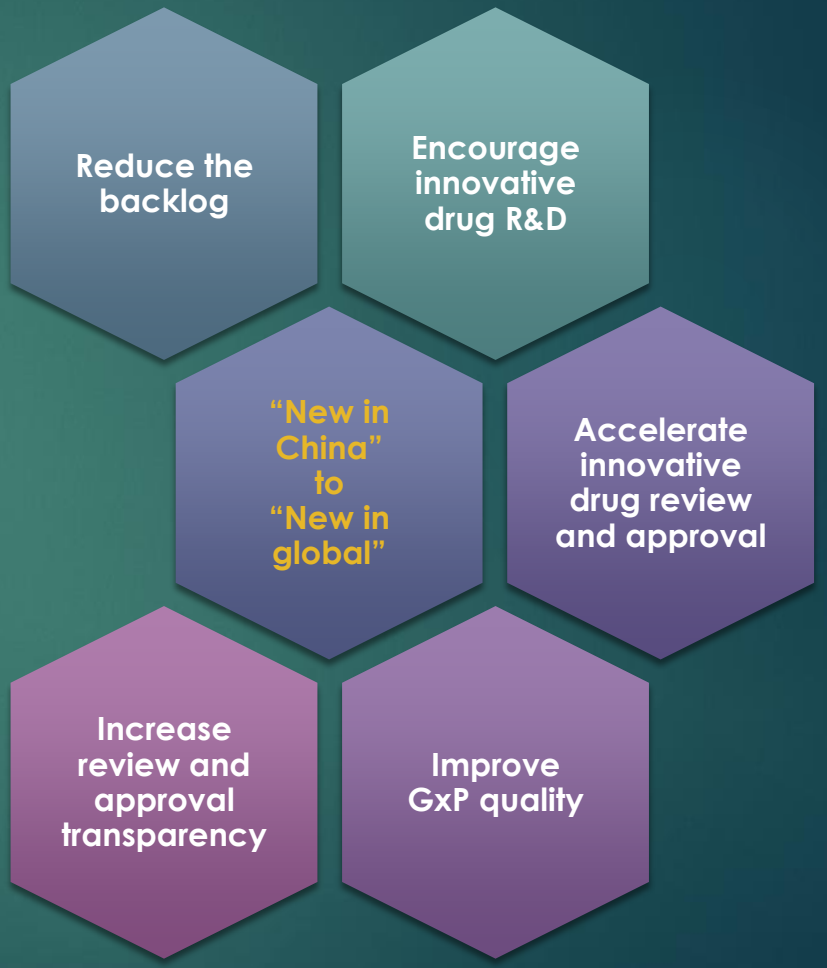
Revision of
Drug Administration Law & Drug Registration Regulation

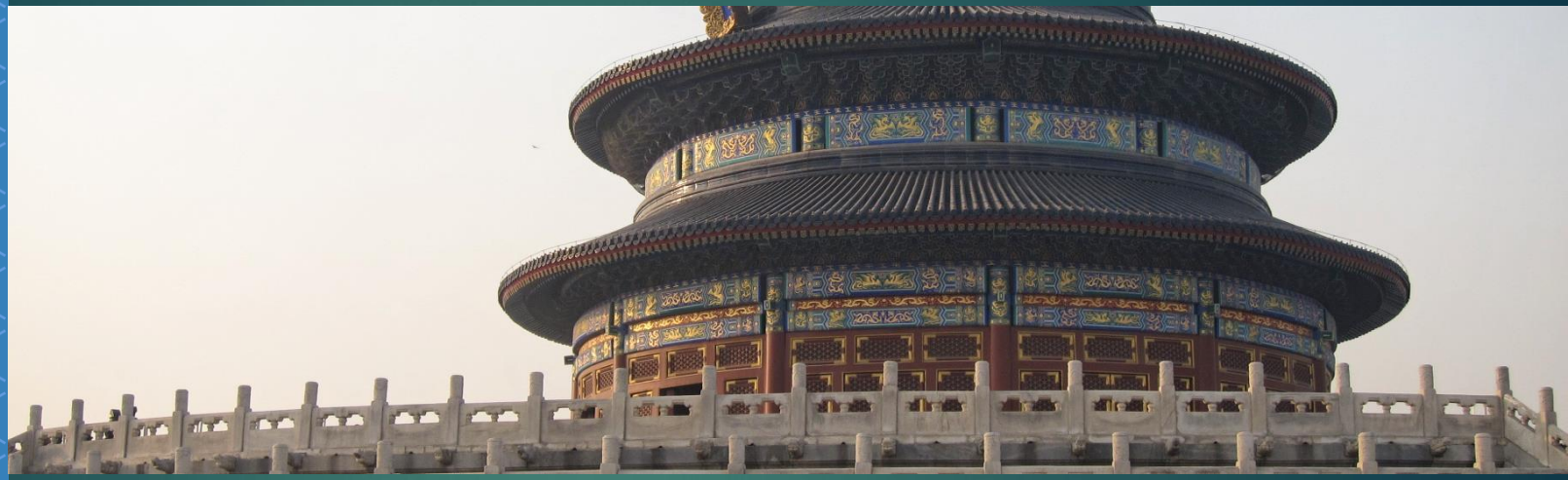
Encourage Innovation	Promote Drug Quality	Enhance Supervision	Streamline Review & Approval	Transparency
• New Chemical Drug Registration Classification • Priority review • Registration technical requirement • MAH Pilot	• Generic Consistency Evaluation • Chinese Pharmacopeia	• Clinical Study on-site Inspection • GMP Inspection (Domestic & Oversea) • Distribution administration	• Filing for BE studies • Work procedure for clinical study on-site inspection • CDE communication meetings • Measures on Advisory	• Communication mechanism for CTA & NDA • Disclose drug evaluation information • Re-evaluation procedure in CDE

Positive General Trend

- New drug definition changes from "New in China" to "**New in global**"

- CNDA has been approved as a new Regulatory Member of **ICH** since June 2017





New Guidance & Guidelines

New Guidance & Guidelines

- 2015.01 Multi-Regional Clinical Trial (Pilot)
- 2015.07 Announcement of Self-inspection on the Clinical Trial Data
- 2015.07 Adverse Drug Reaction Reporting and Monitoring
- 2016.02 Priority Review & Approval Procedure
- 2016.03 New Chemical Drug Registration Classification
- 2016.06 Biostatistics Principles for Clinical Trials
- 2016.06 Communications for Drug Development and Technical Evaluation (Trial)

New Guidance & Guidelines (cont'd)

- 2016.07 Electronic Data Capture for Clinical Trials
- 2016.07 Data Management Planning and Reporting of Statistical Analysis
- 2017.01 General Considerations to Clinical Trials for Drug
- 2017.05 Regulatory Data Protection (Draft for Public Comment)
- 2017.10 Decisions on the Adjustment of Imported Drug Registration
- 2018.01 Implementation of ICH Guidelines
- 2018.07 Technical Guide for Acceptance of Overseas Clinical Trial Data for Drugs

Multi-Regional Clinical Trial (Pilot)
(Key Points)

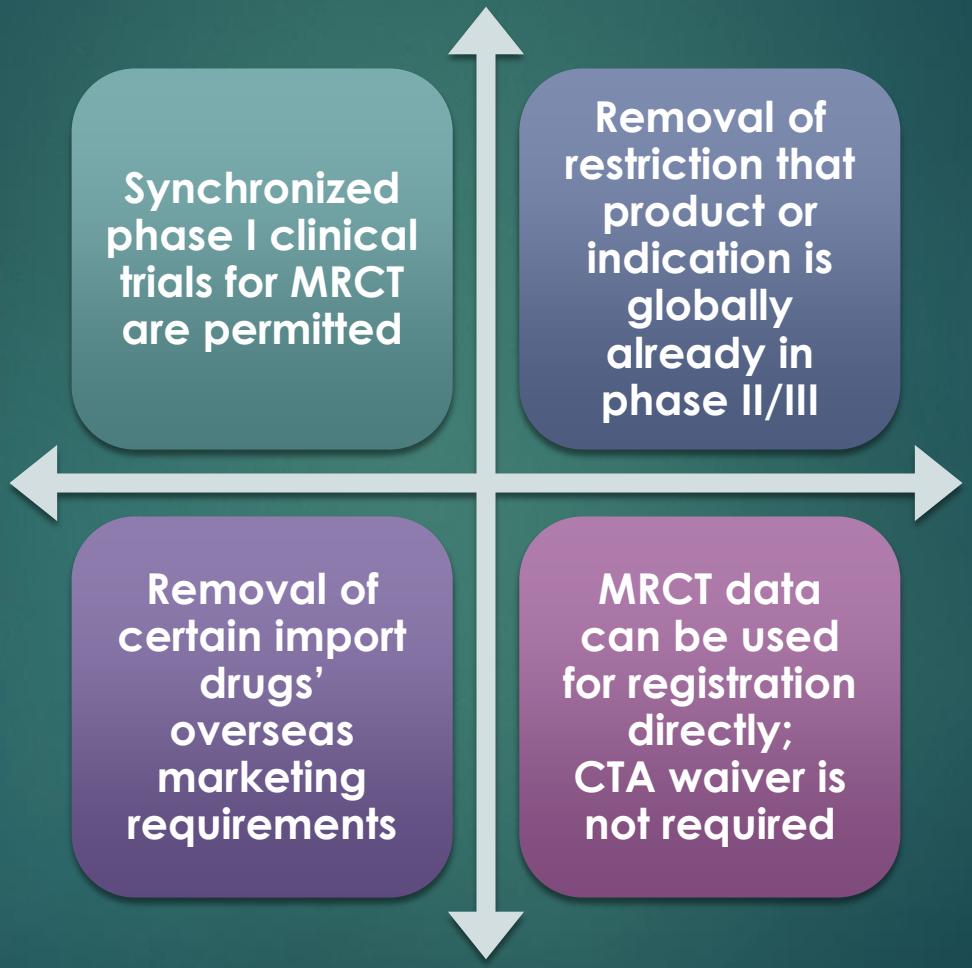
Two Types of Clinical Trials	• The trials performed simultaneously at **multiple centers in different regions** according to the same clinical trial protocol • The **regional trials simultaneously at multiple centers** in different countries within a region for scientific and safety considerations according to the same clinical trial protocol • If the data is used for drug registration in China, it should be derived from at **least two countries (China plus 1 country at least)**
Trend Consistency of Subgroup	• It is required to first develop the statistical methods to evaluate if there is **trend consistency between the subgroup results and the overall results** • With regards to the use of data for drug registration application in China, first, the overall evaluation of the global clinical trial data and then further **trend analysis of the clinical trial data generated in Asia and China** are required

Multi-Regional Clinical Trial (Pilot)
(Key Points)

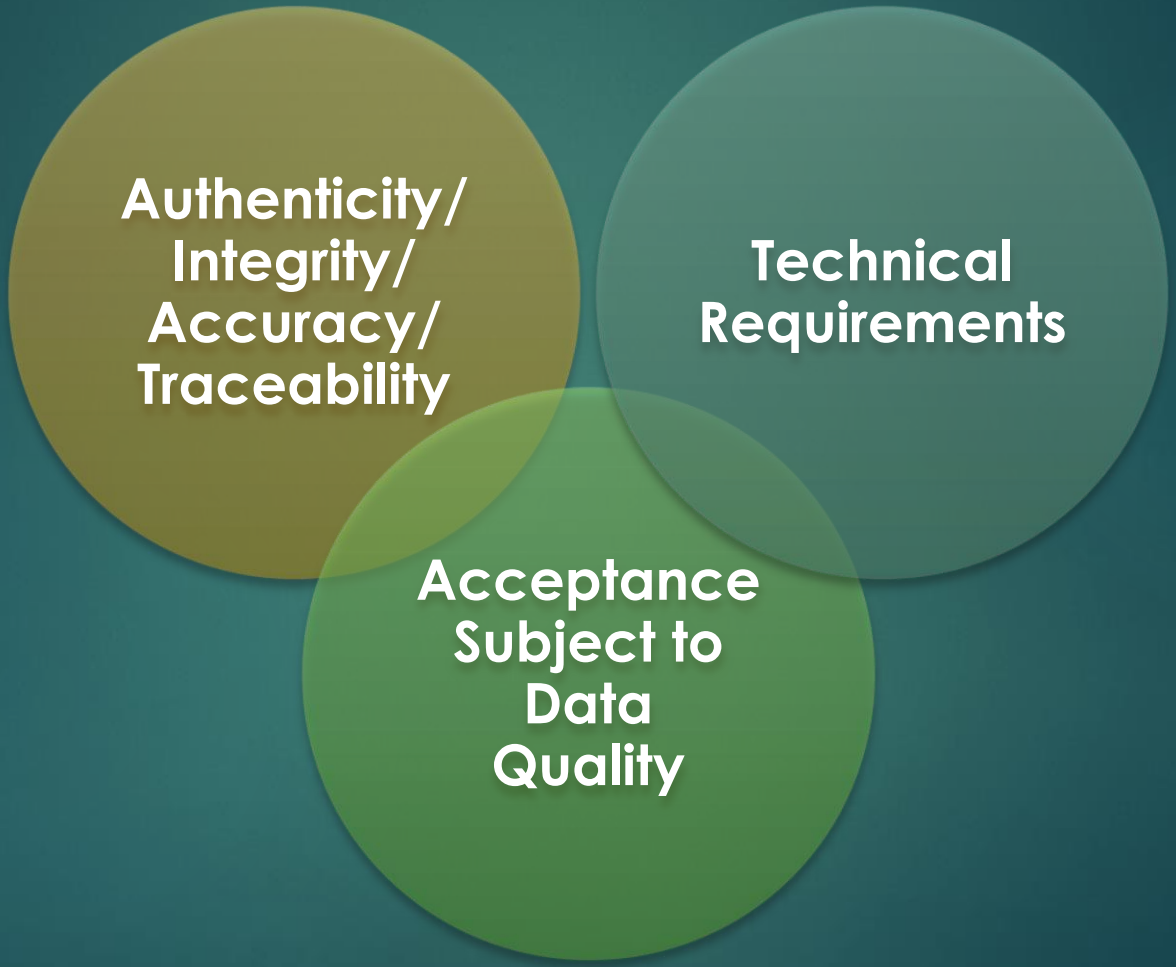
Sample Size Considerations

- Sample size should be reasonably distributed among different countries and centers, and corresponding scientific and legal basis for determination of such distribution should be provided
- When conducting the clinical trials, in addition to satisfaction of the statistics requirements, it is also required to satisfy **the needs for subgroup evaluation** and fully consider the epidemiological characteristics of disease, the representativeness of sample selection and other relevant factors
- Attention is to be paid to whether the **sample size of Chinese subjects is big enough to evaluate and demonstrate the safety and efficacy of the investigational drug for patients in China**

Decisions on the Adjustment of Imported Drug Registration



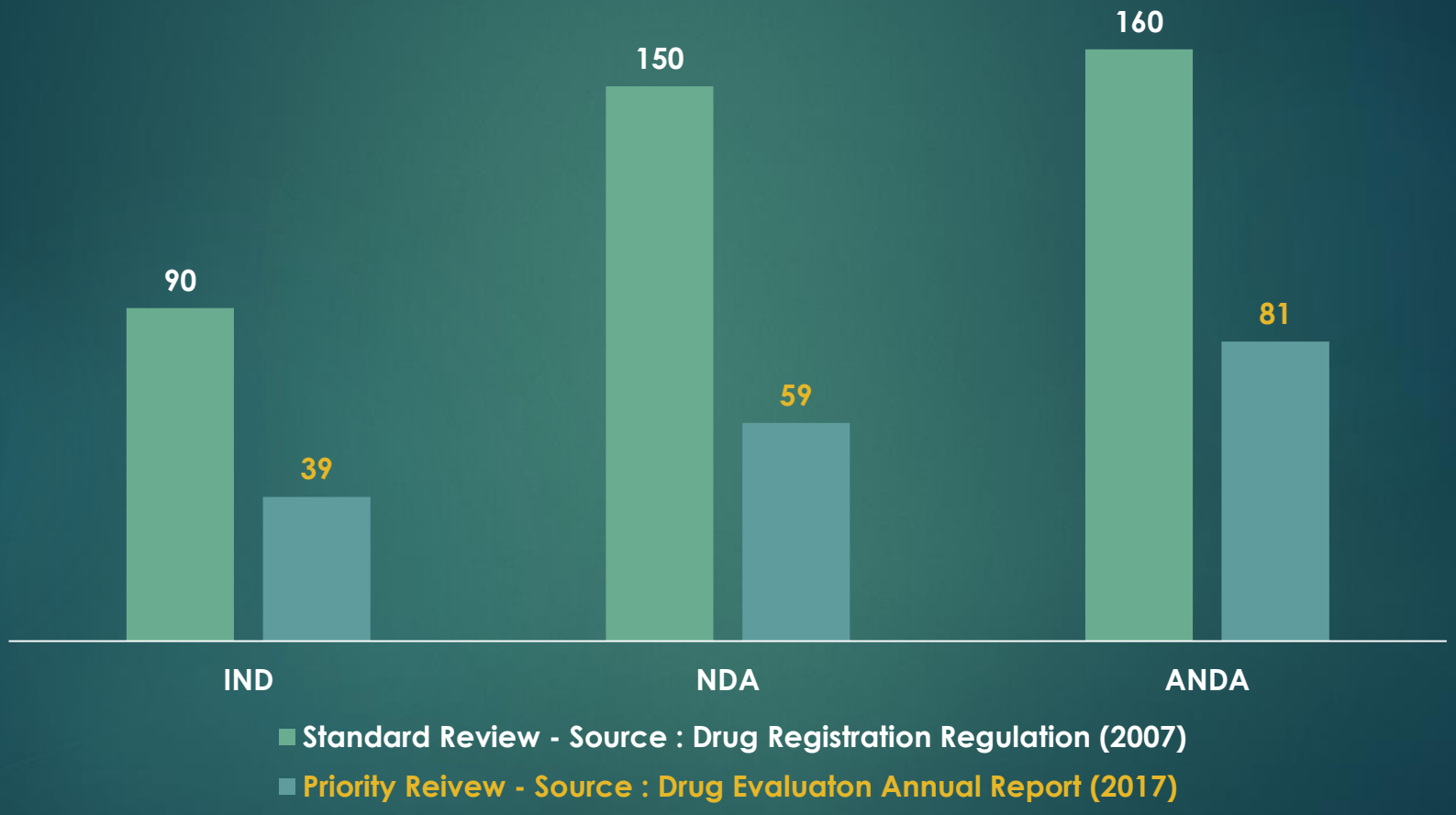
Technical Guide for Acceptance of Overseas Clinical Trial Data for Drugs



Self-Inspection & On-site Inspection

Regulatory Background	• Self-inspection and on-site inspection is **required for all NDA approval as of now** • Sponsors can voluntarily choose to withdraw the NDA if the data reliability and integrity cannot be guaranteed • **All domestic and foreign research centers** participating in the MRCT should accept the on-site inspections organized by CNDA
Data Fraud Consequence	• If data integrity is questioned, this would result in rejection of the NDA • **Data fraud is treated as a criminal felony** and will result in **penalties** including ✓ Ban of submission of the same application within 3 years ✓ Any other submission by the same sponsor within 1 year ✓ No other NDA approval would be granted to the sponsor during this time

Priority Review & Approval
(Working Days of Evaluation)



Priority Review & Approval (cont'd)

Drugs with significant clinical value	• **Innovative drugs not yet marketed anywhere** • Innovation drugs transferred to China for local manufacture • Drugs with advanced formulation technologies, or innovative therapies, or **substantial clinical advantage** • CTA submission within 3 years before patent expiry and NDA within one year before patent expiry • **Simultaneous IND** (approved in US/EU); NDA for local manufacture (under review in EU or US and passing GMP/GCP inspection) • Traditional Chinese Medicine with clear clinical therapeutic purpose in prevention and treatment for major diseases • New drug listed in the Specific National Program
Drugs with significant clinical advantage	• AIDS, TB, Viral hepatitis, **Rare disease**, Cancer, **Pediatric**, Geriatric
Others	• Drugs in **urgent clinical demand** & shortage of market supply (list finally determined by CDE)

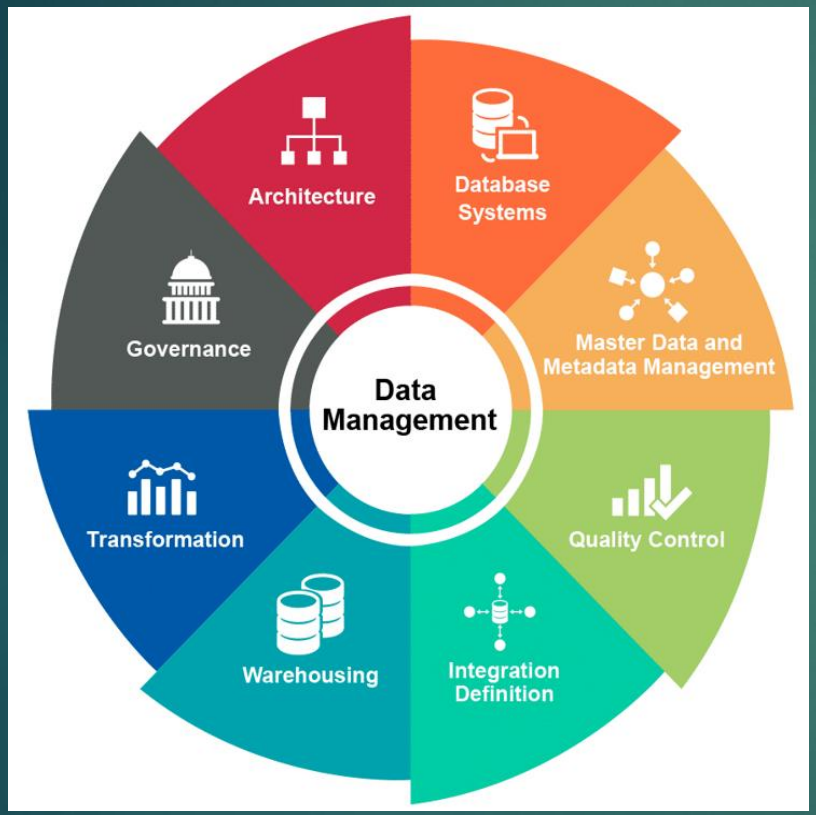
New Chemical Drug Registration Classification

Registration Classification		Category Description
New Drugs	**1**	**Innovative drugs not marketed at home and abroad**
	2	**New improved drugs that are not marketed at home and abroad**
Generics	3	Imitation of original drugs that are marketed overseas but unavailable domestically
	4	Imitation of original drugs that are marketed domestically
Imported Drugs	5.1	Application for the domestic marketing authorization of original drugs marketed overseas
	5.2	Application for the domestic marketing authorization of non-original drugs marketed overseas

Formal Consultation Meetings with CDE
(Trial)

Type I	• A meeting that is necessary for **solving an critical issue** in clinical trials of an innovative drug or to address an important safety issue
Type II	• Meeting **at a critical development stage** ✓ Pre-Phase I ✓ End of Phase II ✓ Pre-Phase III ✓ Pre-NDA • Risk Evaluation and Management Meeting pre-NDA approval
Type III	• Any meeting **other than Type I or Type II** of new drug, and critical issues in the development of improved new drugs and generic drugs

Data Management Planning and Reporting of Statistical Analysis



Data Management Plan (DMP)

- Study Overview
- Roles & Responsibilities
- Type, format, source and flow of study data
- Systems employed in data collection, management and integration
- Data management documentation, activities and operation procedures
- Quality assurance quality control systems
- **Blind Review**

Data Management Planning and Reporting of Statistical Analysis (cont'd)

(**D**ata **M**anagement **R**eport - China Specific)

Execution process & major time points	Operation practice and quality of data management	Participating entities and responsibilities
CRF, database design & external data management	Data quality assurance & data validation and cleaning	Medical coding
Data transmission record of major time points	Version change record of critical documents	Deviations from DMP

Data Management Planning and Reporting of Statistical Analysis (cont'd)

Statistical Analysis Plan (SAP)

- Type of design and comparison
- Randomization and blinding method
- Definition and measurement of primary and secondary indicators
- Test hypothesis
- Definition of analysis set
- Plan for efficacy and safety evaluation and statistical analysis
- Principles for the analysis of primary indicators and expected method of analysis for confirmatory trials
- Generalized principles and methods for explanatory trials

Data Management Planning and Reporting of Statistical Analysis (cont'd)

(**S**tatistical **A**nalysis **R**eport - China Specific & in Chinese)

- Key information from CSR
- Raw and analysis database and variable description
- Flow chart of subject distribution
- Randomization scheme
- Blind Review Resolution
- Statistical charts and tables supplementary to the main text
- SAS codes for non-standard statistical methodologies
- Published literature of statistical methods for non-standard statistical methodologies

Schedule of eCTD implementation in CDE

Regulatory Data Protection
(Draft for Public Comment)

Innovative Drugs

Innovative Treatment of Rare Diseases

Innovative Treatment of Pediatric Uses

Innovative Therapeutic Biologics

ICH Guidelines Implementation

2018.02.01	2018.05.01	2018.07.01	2019.07.01 (Optional) 2022.07.01 (Mandatory)
Registration Application	**Clinical Development Adverse Events Monitoring**	**Post Approval Adverse Events Monitoring**	**Post Approval Adverse Events Monitoring**
M4 The Common Technical Document	M1 MedDRA Terminology E2A & E2B(R3) Clinical Safety Data Management	E2D Post-Approval Safety Data Management	M1 MedDRA Terminology E2B(R3) Clinical Safety Data Management

Adverse Drug Reaction Reporting & Monitoring
(**P**ost **A**pproval **S**afety **S**urveillance)

Regulatory Background	• All companies must implement an intensive monitoring procedure • Publication and Implementation of final guidance in 2015
Technical Requirement	• Requires non-interventional study protocol submitted within 60 working days of receiving approval certificate • **Data on at least 3000 patients within 5 year license period; For rare diseases, 80% of patients administered with study drug** • **Real world setting** including hospital, community medical service institution, drugstore, family planning station, drug rehabilitation center, and other drug using units
Summary Report	• Submit CSR to Adverse Drug Reaction group within 5 year and before license renewal • **Failure to comply leads to rejection of license renewal or withdrawal**

Entresto™ CFDA Submission Case Study

Key Value

Entresto™ offers superior outcomes versus ACE inhibitors

- **20% reduction in CV mortality**
- **21% reduction in HF hospitalization**

Entresto™ IS the new foundation of care that symptomatic HFrEF patients should not be without

THAT offers superior outcomes versus ACE inhibitors

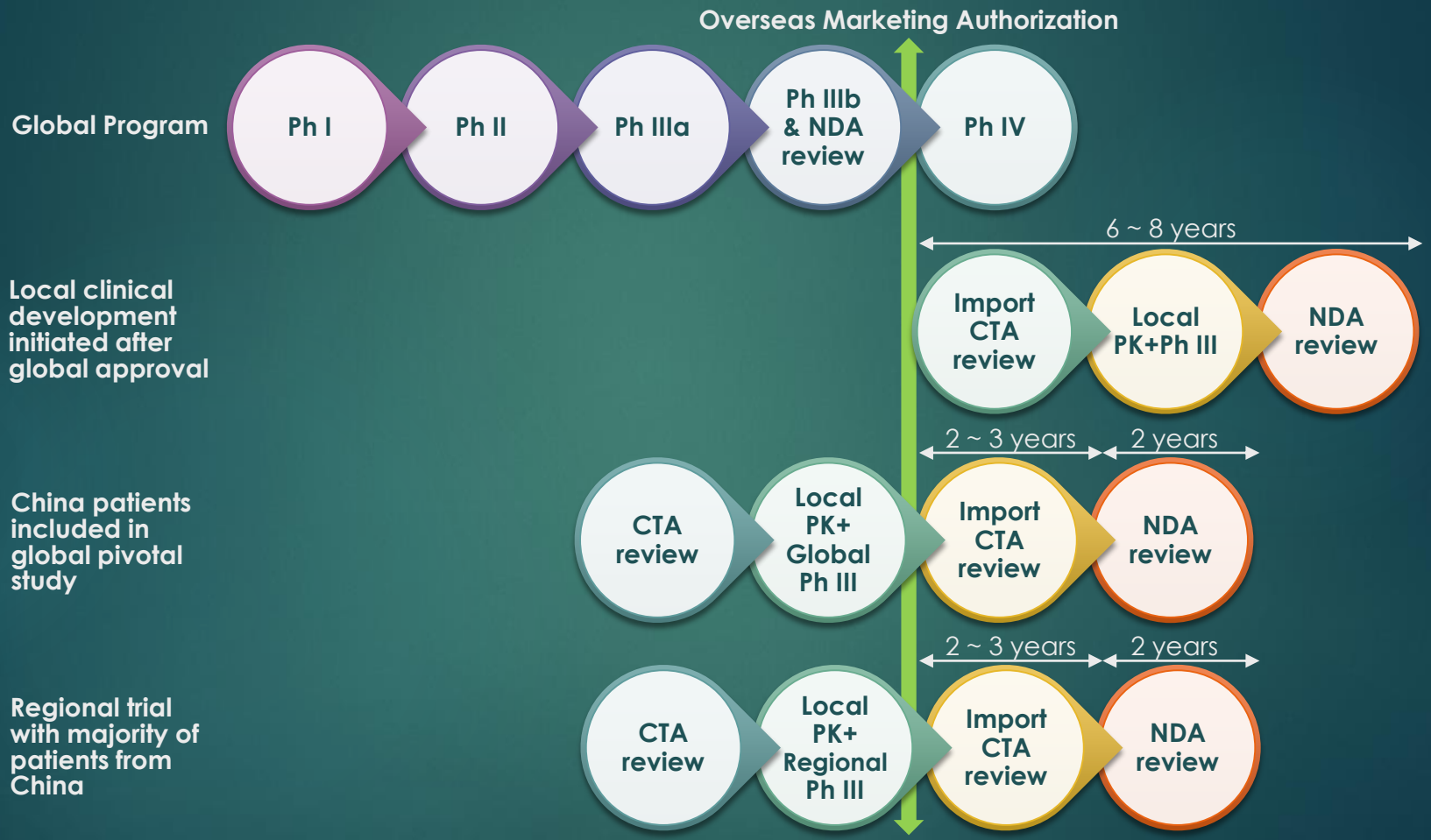
BECAUSE of its novel mechanism of action

Entresto™ helps keep HFrEF patients living longer, out of the hospital, and feeling better

Primary Efficacy Evaluation
(Endpoint - CV mortality or HF Hospitalization)

	Overall Population	China Population	Chinese Population	Asian Population
Hazard Ratio (95% CI)	0.80 (0.73–0.87)	**0.95 (0.63–1.44)**	0.86 (0.62-1.19)	0.82 (0.63-1.07)

Development Strategies Pursued in China



Milestones of Submission

2015

- **Mar 29** Pre-NDA meeting with CDE
- **Jul 8 FDA approval of Entresto™**
- **Oct 21** Submission of post-CPP CTA

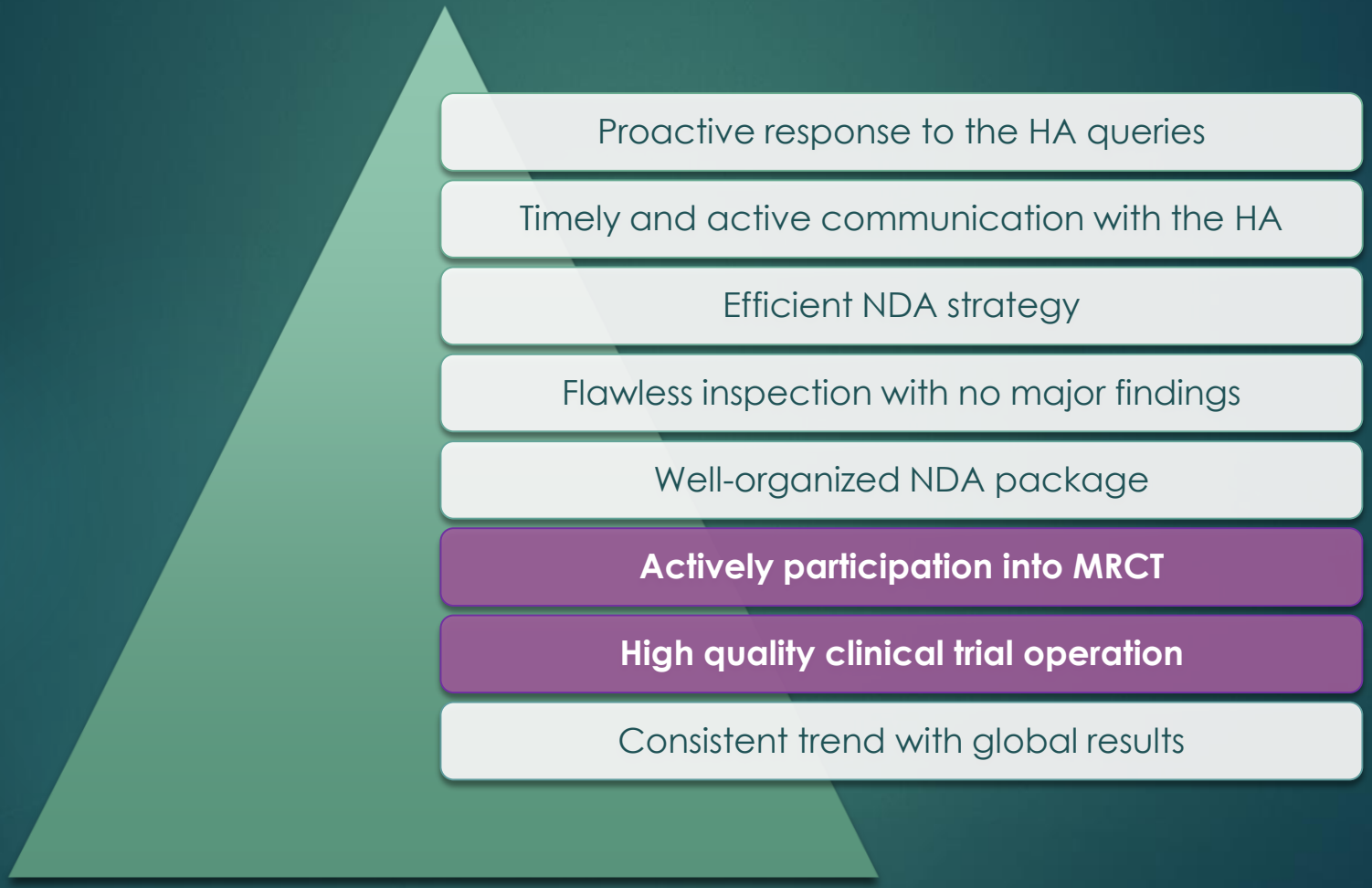
2016

- **Jan 26** CFDA approval of CTA with conclusion of clinical trial waiver
- **Mar 2** Submission of NDA
- **Mar 17** Submission of priority review application
- **Sep 21** Submission of self-inspection results
- **Dec 12 CFDA approval of priority review**
- **Dec 19** Submission of on-site inspection acceleration request

2017

- **Apr 26 Completion of on-site inspection**
- **May 14** On-site inspection report transfer to CDE
- **Jul 24** Highest level CFDA approval meeting
- **Jul 28 CFDA approval of Entresto™**

Key Factors to Submission Success



Summary

Significant Improvement of Regulatory Environment

- CTA timelines shortened from average of 2 years to 4-5 months;
  In the future, 60 wds under the filing mechanism announced Jul 27, 2018
- Shorter and predictable approval timelines
- More flexible with regards to local clinical data
- Simultaneous development and approval with US/EU
- ICH aligned technical requirements to promote clinical trial quality and be consistent with global standards

Links

Multi-Regional Clinical Trial (Pilot)

Announcement of Self-inspection on the Clinical Trial Data

Intensive Post Approval Safety Surveillance

Priority Review & Approval Procedure

New Chemical Drug Registration Classification

Biostatistics Principles for Clinical Trials

Communications for Drug Development and Technical Evaluation

Electronic Data Capture for Clinical Trials

Data Management Planning and Reporting of Statistical Analysis

General Considerations to Clinical Trials for Drug

Data Protection Regime (Draft for Public Comment)

Decisions on the Adjustment of Imported Drug Registration

Implementation of ICH Guidelines

Implementation of eCTD

Technical Guide for Acceptance of Overseas Clinical Trial Data for Drugs

Adjustment of Evaluation and Approval of Drugs Clinical Trial Application

Backup

Sample Size Requirement for China Registration in the Past

	Local R&D	Imported Drug
PK study/ Phase I	>=20-30 for Phase I 	>=20-30 for PK study 
Phase II	>=100 on test drug 	
Phase III	>=100 on each arm for small molecules  >=300 on test drug for biologics 	
Phase IV	>=2000 on test drug 	

Multi-Regional Clinical Trial (Pilot)
(Subgroup Definition)

China Population		**Patients recruited from sites in mainland China**
Chinese (-Originated) **Population**		**Patients of Chinese ethnicity**
(East-)**Asian Population**		**Patients recruited from sites in Asia excluding India and West Asia**

Multi-Regional Clinical Trial (Pilot)
(Key Points) (cont'd)

CTA Documents	• The sponsor should submit the application dossier which has been submitted to the regulatory authorities in the countries with developed pharmaceutical industry (such as ICH member countries), including the full clinical trial protocol (including trial protocol numbers) and supporting data
CSR	• The clinical trial report should first summarize and analyze the overall global clinical trial data and then compare the efficacy and safety data of **Asian** populations with that of **non-Asian** populations and conduct **trend analysis** thereof • It should also compare the efficacy and safety data of China population with non-China population and conduct trend analysis thereof

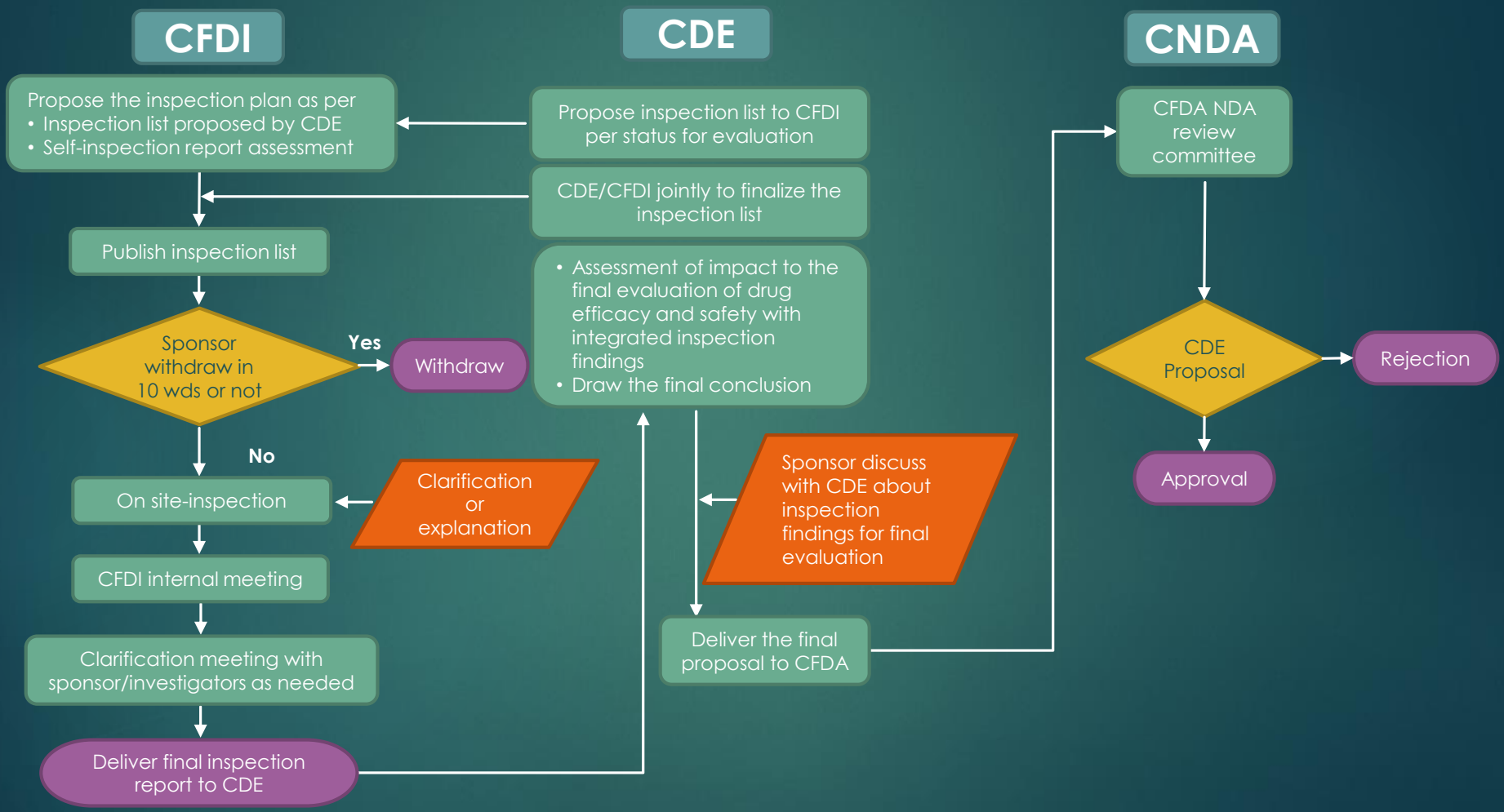
Multi-Regional Clinical Trial (Pilot)
(Key Points) (cont'd)

Protocol Amendment	• Amendment with significantly impact on the safety of subjects, significantly change to the risk/benefit ratio of the clinical trial, or cause substantial increase in the number of subjects enrolled in China, the sponsor should submit supplementary application to the CFDA and may not implement such amendment until the CFDA approval is obtained
Scientific Considerations on Protocol Design	• Disease epidemiology • Differences in medical practice • Differences in drug metabolism • Dose selection • Selection of control drug • Efficacy evaluation indicators • Sample size considerations • Other statistical considerations • Collection and evaluation of adverse events/reactions • Other considerations

Multi-Regional Clinical Trial (Pilot)
(Key Points) (cont'd)

Comparator Selection	• Should consider its approved indications, availability and usage in the relevant countries and regions • Besides, where different treatment guidelines are adopted, and different therapeutic drugs are used as the gold standard, it is required to expound and prove the basis of determination of the control drug • If the placebo is used as control, the different approval principles and standards of the ethics committees in different countries and regions should be considered
IDMC/EAC	• With regards to the studies with more than **20%** Chinese patients number, it is suggested to include **China experts** into the global IDMC • With regards to the studies with more than **20%** Chinese patients number, it is suggested to include the **China experts** into the design and discussion of the clinical trial protocol

Self-Inspection & On-site Inspection
(CNDA Inspection Process Overview)



Priority Review & Approval (cont'd)
(Process & Timeline)

Request	•On-line application after CDE received the dossier
Grant	•Monthly panel meeting and publish the agreed priority list for public comments •The priority review will be granted if no objection within 5 wds
CDE Technical Review	•CDE starts the review in 10 wds •GMP & GCP site inspection could be accelerated
Technical Report Transfer	•Complete Review Report within 5 wds after receipt of the site inspection report •Report is to be transferred to CFDA for final review and approval within 3 wds
Approval	•CFDA approval in 10 wds after receiving documents from CDE •Conditional approval could be granted prior to the completion of phase III confirmatory trial for life threatening diseases with no effective treatment

Blind Review
(China Specific)

Practices

- Verification and assessment to data prior to unblinding but post LPLV to make a final decision to SAP
- Determine severity of protocol deviations
- Review safety data
- Explain to the questions about site performance
- Prepare for DBL
- Decide FAS and PPS datasets and prepare **Blind Review Resolution**
- Prepare final SAP

Related Data

- Major Protocol Deviation
- Adverse Event listing
- Concomitant Medication listing
- Data listing of early termination
- Data listing of Abnormal lab data with clinical significant

Technical Guide for Acceptance of Oversea Clinical Trial Data for Drugs

Authenticity/ Integrity/ Accuracy/ Traceability	• Applicable to innovative drugs as well as generic drugs • **Compliant with ICH GCP** in the lifecycle of data generation • Entire overseas clinical trial data must be provided for China registration,
Technical Requirements	• Domestic/overseas clinical trial data should be fully summarized and organized in a package following Drug Registration Regulation • Data of Biopharmaceutics, Pharmacology, Safety and Efficacy are inclusive • **CTD format** is recommended
Acceptance Subject to Data Quality	• Data is authentic and reliable; compliant with DRR; sufficient to support evaluation of safety and efficacy; with no impact on safety and efficacy due to ethnical sensitivity is **fully acceptable** • Data with uncertainty in extrapolation of safety and efficacy on China population or data with impact on safety and efficacy due to ethnical sensitivity is **partially acceptable** • Data insufficient to support evaluation of safety and efficacy or data with significant issues is **unacceptable** • Data for drug registration for life-threatening disease, rare disease or pediatric with no effective treatment is **conditionally acceptable** even if it was partially acceptable

Other Requirements/Guidance

Study Data Standardization Plan	• Not yet required
Annotated CRF	• Mandatory
Source & Analysis Data	• **CDISC recommended** but not yet mandated
CDISC compliance checks	• Recommended to do the same as for FDA
Data Reviewer's Guide	• Not yet required
Define.xml	• Not yet required but need a text file containing brief introduction of deliverables
Programs	• Not yet required

Pros/Cons of Clinical Trial Strategies

	Advantages	Disadvantages
China in Global	• **Budget and timeline optimal** • **Quickest access to new drug** • Mitigate lack of power in China subset if clinical need plus consistent positive trend in data	• China subset typically not statistically powered • **Limited by timeline of China CTA & global phase III recruitment** • FDA may not accept global studies dominated by China subjects
China Regional	• Acceptable approach if insufficient China subjects in the global program	• Enough China subjects to ensure adequate power • Larger sample size • Considerable loss in time to market • Additional cost
China Alone	• Traditional approach • Acceptable to CFDA	• Slowest approach – start when drug is approved in US/Europe • Usually requires Active comparator

Arigatou gozaimasu.

ありがとうございます

[thank you very much]