New CFDA Requirements and its Implementation

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- 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
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
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**
- New Chemical Drug Registration Classification
- Priority review
- Registration technical requirement
- MAH Pilot

**Promote Drug Quality**
- Generic Consistency Evaluation
- Chinese Pharmacopeia

**Enhance Supervision**
- Clinical Study on-site Inspection
- GMP Inspection (Domestic & Oversea)
- Distribution administration

**Streamline Review & Approval**
- Filing for BE studies
- Work procedure for clinical study on-site inspection
- CDE communication meetings
- Measures on Advisory

**Transparency**
- 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

- Reduce the backlog
- Encourage innovative drug R&D
- "New in China" to "New in global"
- Accelerate innovative drug review and approval
- Increase review and approval transparency
- Improve GxP quality
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)
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
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

- Synchronized phase I clinical trials for MRCT are permitted
- Removal of restriction that product or indication is globally already in phase II/III
- Removal of certain import drugs’ overseas marketing requirements
- MRCT data can be used for registration directly; CTA waiver is not required
Technical Guide for Acceptance of Overseas Clinical Trial Data for Drugs

Authenticity/Integrity/Accuracy/Traceability

Technical Requirements

Acceptance Subject to Data Quality
# 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)

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

<table>
<thead>
<tr>
<th>Registration Classification</th>
<th>Category Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Innovative drugs not marketed at home and abroad</td>
</tr>
<tr>
<td>2</td>
<td>New improved drugs that are not marketed at home and abroad</td>
</tr>
<tr>
<td><strong>Generics</strong></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Imitation of original drugs that are marketed overseas but unavailable domestically</td>
</tr>
<tr>
<td>4</td>
<td>Imitation of original drugs that are marketed domestically</td>
</tr>
<tr>
<td><strong>Imported Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>5.1</td>
<td>Application for the domestic marketing authorization of original drugs marketed overseas</td>
</tr>
<tr>
<td>5.2</td>
<td>Application for the domestic marketing authorization of non-original drugs marketed overseas</td>
</tr>
</tbody>
</table>
### Formal Consultation Meetings with CDE (Trial)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>A meeting that is necessary for solving an <strong>critical issue</strong> in clinical trials of an innovative drug or to address an important safety issue</td>
</tr>
<tr>
<td>Type II</td>
<td><strong>Meeting at a critical development stage</strong>&lt;br&gt;✓ Pre-Phase I&lt;br&gt;✓ End of Phase II&lt;br&gt;✓ Pre-Phase III&lt;br&gt;✓ Pre-NDA&lt;br&gt;<strong>Risk Evaluation and Management Meeting pre-NDA approval</strong></td>
</tr>
<tr>
<td>Type III</td>
<td>Any meeting <strong>other than Type I or Type II</strong> of new drug, and critical issues in the development of improved new drugs and generic drugs</td>
</tr>
</tbody>
</table>
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)
(Data Management Report - 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
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)

(Statistical Analysis Report - 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

- **2018.06** Invitation for bidding
- **2018.07** Bidding Closed
- **2018.08** Contract Signed
- **2018.12** System pre-check
- **2019.03** System roll-out
Regulatory Data Protection
(Draft for Public Comment)

- **6 years** Innovative Drugs
- **10 years** Innovative Treatment of Rare Diseases
- **10 years** Innovative Treatment of Pediatric Uses
- **10 years** Innovative Therapeutic Biologics
ICH Guidelines Implementation

- **2018.02.01**
  - Registration Application
  - **M4**
    - The Common Technical Document

- **2018.05.01**
  - Clinical Development
    - **Adverse Events Monitoring**
    - **M1**
      - MedDRA Terminology
      - **E2A & E2B(R3)**
        - Clinical Safety Data Management

- **2018.07.01**
  - Post Approval
    - **Adverse Events Monitoring**
    - **E2D**
      - Post-Approval Safety Data Management

- **2019.07.01 (Optional)**
- **2022.07.01 (Mandatory)**
  - Post Approval
    - **Adverse Events Monitoring**
    - **M1**
      - MedDRA Terminology
      - **E2B(R3)**
        - Clinical Safety Data Management
## Adverse Drug Reaction Reporting & Monitoring
(\textit{Post Approval Safety Surveillance})

<table>
<thead>
<tr>
<th><strong>Regulatory Background</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• All companies must implement an intensive monitoring procedure</td>
</tr>
<tr>
<td>• Publication and Implementation of final guidance in 2015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Technical Requirement</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Requires non-interventional study protocol submitted within 60 working days of receiving approval certificate</td>
</tr>
<tr>
<td>• \textbf{Data on at least 3000 patients within 5 year license period; For rare diseases, 80% of patients administered with study drug}</td>
</tr>
<tr>
<td>• \textbf{Real world setting} including hospital, community medical service institution, drugstore, family planning station, drug rehabilitation center, and other drug using units</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Summary Report</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Submit CSR to Adverse Drug Reaction group within 5 year and before license renewal</td>
</tr>
<tr>
<td>• \textbf{Failure to comply leads to rejection of license renewal or withdrawal}</td>
</tr>
</tbody>
</table>
Entresto™ CFDA Submission Case Study
**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)

- **Entresto™ n/N (%)**
- **Comparator n/N (%)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Entresto™</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Population</td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>China Population</td>
<td>25%</td>
<td>27%</td>
</tr>
<tr>
<td>Chinese Population</td>
<td>28%</td>
<td>32%</td>
</tr>
<tr>
<td>Asian Population</td>
<td>24%</td>
<td>28%</td>
</tr>
</tbody>
</table>

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

**Global Program**
- Ph I
- Ph II
- Ph IIIa
- Ph IIIb & NDA review
- Ph IV

**Local clinical development initiated after global approval**

**China patients included in global pivotal study**

**Regional trial with majority of patients from China**

**Overseas Marketing Authorization**
- 6 ~ 8 years

- Import CTA review
- Local PK+Ph III
- NDA review

- 2 ~ 3 years
- 2 years

- CTA review
- Local PK+ Global Ph III
  - Import CTA review
  - NDA review
  - 2 ~ 3 years
  - 2 years

- CTA review
- Local PK+ Regional Ph III
  - Import CTA review
  - NDA review
  - 2 ~ 3 years
  - 2 years
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

- Proactive response to the HA queries
- Timely and active communication with the HA
- Efficient NDA strategy
- Flawless inspection with no major findings
- Well-organized NDA package
- Actively participation into MRCT
- High quality clinical trial operation
- Consistent trend with global results
### 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
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

<table>
<thead>
<tr>
<th>Phase</th>
<th>Local R&amp;D</th>
<th>Imported Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK study/Phase I</td>
<td>&gt;=20-30 for Phase I</td>
<td>&gt;=20-30 for PK study</td>
</tr>
<tr>
<td>Phase II</td>
<td>&gt;=100 on test drug</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>&gt;=100 on each arm for small molecules</td>
<td>&gt;=300 on test drug for biologics</td>
</tr>
<tr>
<td>Phase IV</td>
<td>&gt;=2000 on test drug</td>
<td></td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>CTA Documents</th>
<th>• 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</th>
</tr>
</thead>
</table>
| 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)

**CFDI**
- Propose the inspection plan as per
  - Inspection list proposed by CDE
  - Self-inspection report assessment
- Publish inspection list
- Sponsor withdraw in 10 wds or not
  - Yes: Withdraw
  - No: On site-inspection
  - CFDI internal meeting
  - Clarification meeting with sponsor/investigators as needed
- Deliver final inspection report to CDE

**CDE**
- Propose inspection list to CFDI per status for evaluation
- CDE/CFDI jointly to finalize the inspection list
  - Assessment of impact to the final evaluation of drug efficacy and safety with integrated inspection findings
  - Draw the final conclusion
  - Sponsor discuss with CDE about inspection findings for final evaluation
- Deliver the final proposal to CFDA

**CNDA**
- CFDA NDA review committee
- CDE Proposal
  - Approval
  - Rejection
<table>
<thead>
<tr>
<th>Request</th>
<th>• On-line application after CDE received the dossier</th>
</tr>
</thead>
</table>
| 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 ethical 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 ethical 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

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Data Standardization Plan</td>
<td>Not yet required</td>
</tr>
<tr>
<td>Annotated CRF</td>
<td>Mandatory</td>
</tr>
<tr>
<td>Source &amp; Analysis Data</td>
<td>CDISC recommended but not yet mandated</td>
</tr>
<tr>
<td>CDISC compliance checks</td>
<td>Recommended to do the same as for FDA</td>
</tr>
<tr>
<td>Data Reviewer’s Guide</td>
<td>Not yet required</td>
</tr>
<tr>
<td>Define.xml</td>
<td>Not yet required but need a text file containing brief introduction of deliverables</td>
</tr>
<tr>
<td>Programs</td>
<td>Not yet required</td>
</tr>
</tbody>
</table>
## Pros/Cons of Clinical Trial Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| 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]