Reform of Biological Products Review with a Focus on CMC

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WCBP， Jan 2018

Outline

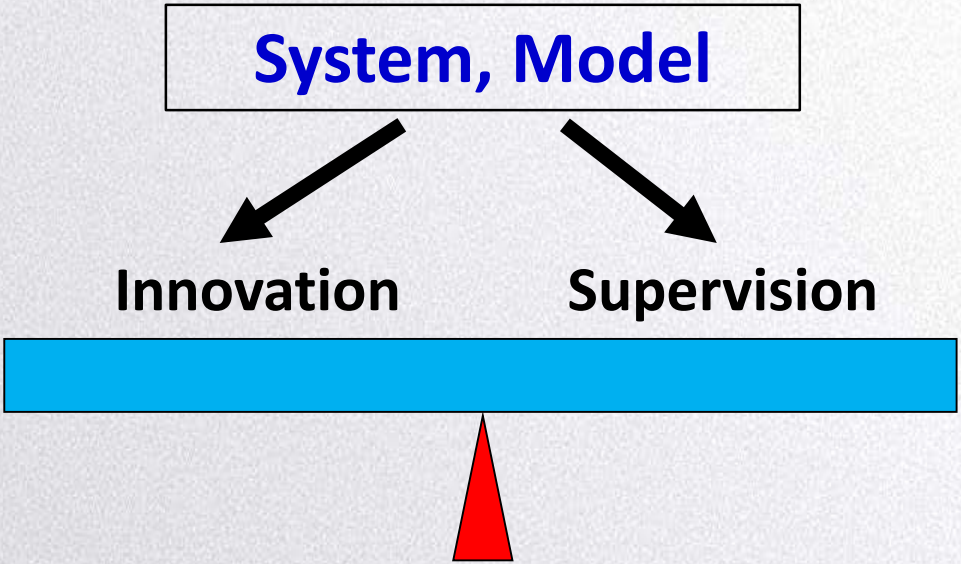
- Background of Drug Review System Reform
- Progress of Reform in the past 2+ years
- Reform Initiatives Focus on CMC

Background of Drug Review System Reform

Status of Biological Product Applications

- **Therapeutic Biologics & Biosimilar**
  - New mAbs: ADC & Bispecific antibody
  - Same target, submitted by multiple applicants
    - Her2, EFFR, CD20
    - PD-1 mAb: 20 applications under development, 3 BLA applications
  - Various R&D levels
- **Vaccine**
  - Vaccine in innovation
    - EV71, sIPV
  - Vaccine in emergency
    - Ebola
  - WHO PQ (prequalification)
- **Cell therapy**
  - CAR-T: **7** applications
  - Transformation from medical technologies to drug development
  - Chinese guideline under development
  - Entrance of Leading companies into China
- **Gene therapy**
  - Plasmid
  - Viral vector
  - Oncolytic virus
- **Blood Products**
- **…**

System, Model, Supervision, Innovation



- To prompt development of innovative drugs;
- To accelerate transformation and upgrading of industry;
- To be in line with international conventions.

Progress of Reform in the past 2+ years

Specific Reform Actions from CDE

Established "Three bases & Seven systems"

Three Bases
✓ Guidance & Standard System for Technical Review
✓ Good Review Practice
✓ Review Information Management System

Seven Systems
✓ Indication based review team
✓ Project management
✓ Communication with applicants
✓ Expert advisory committee
✓ Priority review
✓ Disclosure system of information
✓ Pre-filing review

- **To establish standard and provide guidance**
- **To enhance communications**
- **For a scientific and transparent decisions-making process**

Improve Communication Efficiency

No. 94 Administrative Provisions for Communication about Pharmaceutical Research & Development and Technical Review issued in June 2016

Meeting Type	Purpose of Meeting
Type I	To address major safety issues encountered in the process of clinical trials, and major technical issues of breakthrough therapy drugs in development stage
Type II	Held at the critical stages of innovative drugs development and mainly includes the following situations • Pre-IND meeting • EOP II Meetings • Pre-NDA/BLA Meetings • Meetings for risk evaluation and control
Type III	• Meetings for innovative drugs which are not covered by Type I or Type II meetings • Meetings to address major issues during the development of improved new drugs and generics

- Communication at critical milesones of innovative drug R&D is to jointly solve difficult problems and issues not covered by technical guidelines.
- 500 communication meetings have been held in recent two years to provide support to the development and evaluation of innovative drugs and drugs addressing urgent clinical need.

Establish Expert Advisory Committee

CFDA Administrative Provisions for Expert Advisory Committees for Drug Registration Review, issued in March 2017

Daily consultation	Reviewer can consult with the relevant Expert Advisory Committee members through e-mail, or in writing to solve the technical issues encountered during daily technical review
Expert Consultation Meeting	• Develop or revise technical guidelines and standards • Solve issues in new fields, new technologies, new discoveries & new indications • Resolve the review disputes within CDE • Resolve issues on drug safety, efficacy and quality
Expert Public Hearing	Expert Public Hearing is held to address： • Major technical disputes between review team and applicants • Major public interest issues during the review of drug registration • Major, complex scientific and technical issues

- Explore the mechanisms to solve major disputes, major technical issues during technical review.
- Specify solution to address disputes through expert public hearing.
- Standardize re-review of drug registration.
- Improve the review quality control system.

Criteria of Priority Review Designation

CFDA's Comments on Encouraging Priority Review and Approval for Innovator Drugs issued in Dec 2017

Drugs w/ significant clinical value (Scope)	Drugs w/ significant clinical benefit for (Disease)	Other Criteria
1. Innovative drug not yet marketed anywhere 2. Innovative drug with mfg site transferred to China 3. Drugs with advanced formulation technologies, or innovative therapies, or substantial clinical advantage 4. CTA (3y b/f LoE) and NDA(1y b/f LoE) for patent-off drug 5. Simultaneous IND (approved in US/EU); NDA for local mfg drug (under review in EU or US and passing GMP/GCP inspection) 6. TCM with clear clinical therapeutic purpose in prevention and treatment for major diseases 7. New drug listed in the Specific National Program	1. AIDS 2. TB (Tuberculosis) 3. Hepatitis 4. Rare diseases 5. Malignant tumor 6. Pediatric medicine 7. Diseases with high incidence or unique in elderly people	1. Variation application for process change of generic drug to meet generic quality consistency 2. Re-submitted ANDA to meet generic quality consistency 3. Urgent unmet medical needs and drugs in shortage (listed by HA) 4. Drugs that have been granted compulsory license under the circumstances that the entire public health is subject to serious threats

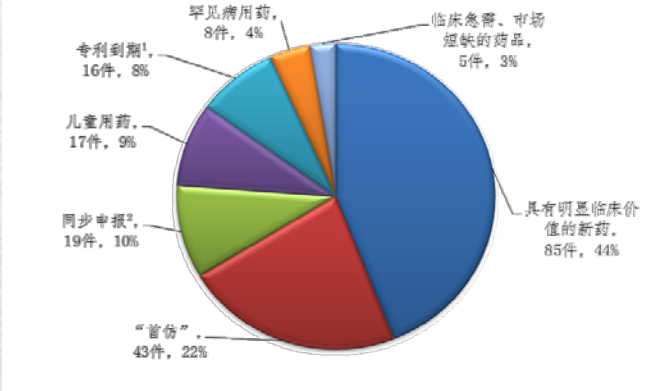
Benefits of Priority Review

- **IND**
  - Apply prior to IND submission and CFDA Feedback within 30 days.
  - Local clinical trial waiver for rare disease or some special disease.
  - Flexible communication.
- **NDA/BLA**
  - Apply prior to NDA/BLA submission and CFDA Feedback within 30 days.
  - Shorten NDA/BLA review timeline.
  - Flexible communication
- **Generic Drug applications**
  - Shorten NDA review timeline.
- **New drugs for severe diseases without effective treatment, or with significant value to meet medical needs**
  - Applicants can apply for F2F communication with CDE any time.
  - Reviewers should arrange meeting to exchange opinions within 10 days.
  - CDE should closely communicate with applicant and guide the clinical development.
  - Conditional approval may be granted when early data show significant clinical value.

Facts of Priority Review Designation

A total of more than 430 applications in 25 batches were granted with the priority review designation, including 36 pediatric drugs (such as: tocilizumab) and 15 drugs for rare diseases (such as: miglustat) .

Jinhua Qinggan Granules	Chidamide
Recombinant Ebola Vaccine	Icotinib
Poliomyelitis Vaccine, Inactivated	Enterovirus Type 71 Vaccine, Inactivated
13Valent :Pneumococcal Conjugate Vaccine	Tocilizumab



Products category of 193 applications which got priority review in 2016

Reform Initiatives Focus on CMC

Reform Focus on CMC review

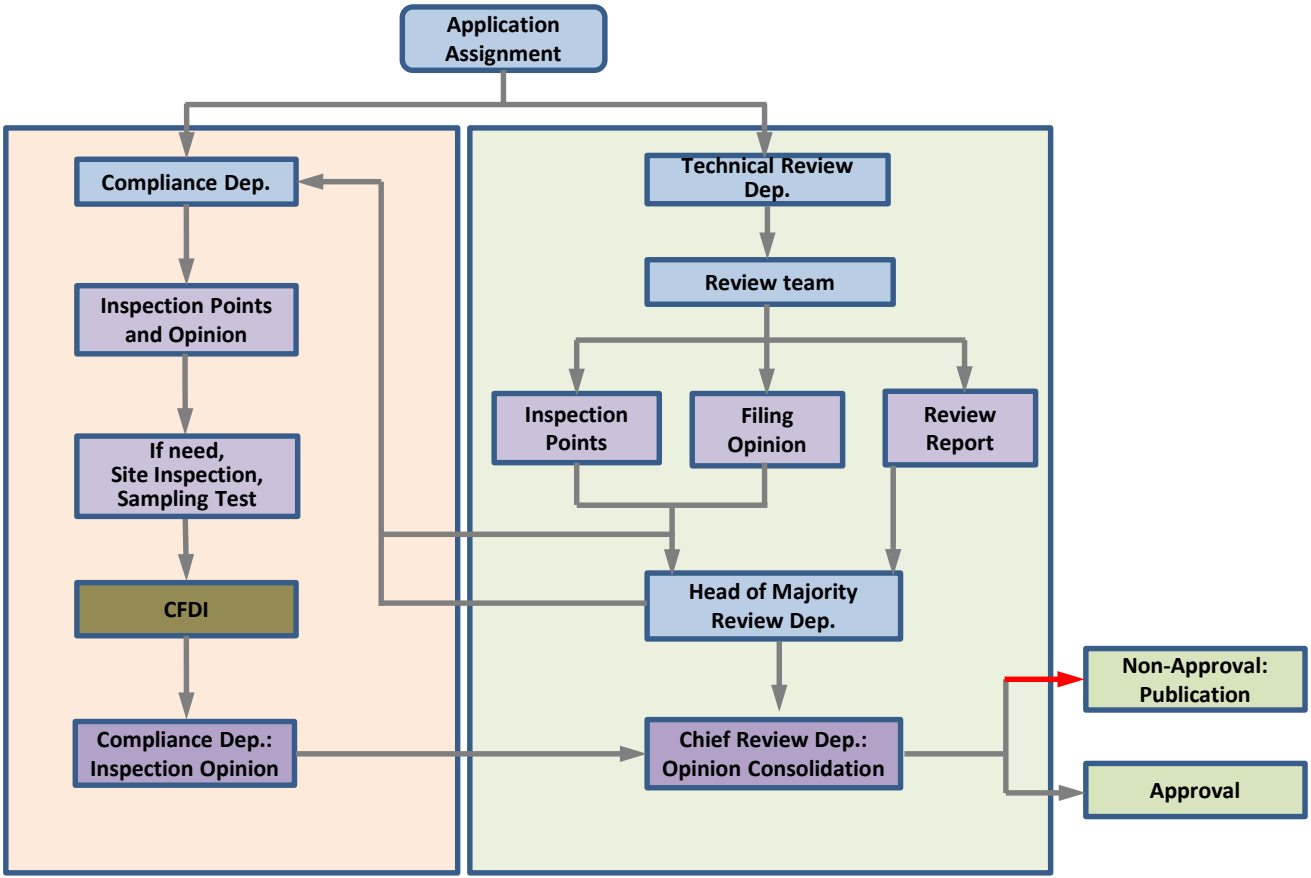
- Adjustment of application procedure
- Joint Review with API, Excipients & Packaging Material
- Change management at clinical stage
- Post-marketing variation management
- Technical guidance for new therapy
  - Biosimilars
  - Cell therapy

Adjustment of Registration Procedure

- Decision of the China Food and Drug Administration on Adjusting the Approval Procedures under the Administrative Approval Items for Certain Drugs (No. 31 of China Food and Drug Administration)
- Announcement on Adjusting Acceptance of Drug Registration Applications (No. 134 in 2017)
- Acceptance:

  Provincial FDA (local products) & Acceptance center of CFDA (imported products) → CDE Centralized Validation (both local and imported products)
- R&D site inspection
- IND sampling testing
  - Based on risk assessment
  - CDE Division of Regulatory Compliance
  - Qualified third parties

HA Review & Approval Process



CFDI: Center for Food and Drug Inspection of CFDA

Overview of Joint Review Policy

Aug 2016: CFDA Announcement (No. 134)	• Establish joint review for packaging material & excipients • Only applied to **local products**
Nov 2016 CFDA Announcement (No. 155)	• Specify dossier requirements for packaging material and excipients
May 2017 CFDA Clarification (No. 134 & No.155)	• Clarify that joint review is not mandatory for CTA, except novel excipient
Nov 2017 CFDA Announcement (No.146)	• Expand scope to **imported drug** • DS (except biologics)/Excipients/Packing material need to get register no. • NDA/ BLA submission need to have Register no. and authorization letter from suppliers
Dec 2017 Draft documents on procedure for joint review	• Change of DS/Excipients/Packaging material may impact DP review • Suppliers should submit annual quality report to CFDA, otherwise register no will be withdrawn • CFDA reserve right for inspection on supplier

IND Review Timeline: 60 working days

- **INDs can go if no rejection or query within 60 working days as of the date of acceptance**
- **How to ensure completion of review within 60 working days**
  - **Improve dossier quality**
    - Technical guidance for first IND application.
  - **Improve communication between applicants and reviewers**
    - Meeting management:
      - ✓ Preparatory meetings
      - ✓ Response to questions in advance
      - ✓ Standardization of meeting minutes.
    - If the data can meet the CTA requirements, IND application can be submitted after consultation meeting.
    - If there are major defects, applicants can submit IND after completing studies.
    - Meeting minutes would be taken as an important evidence for drug R&D, review and approval.

Change Management at clinical stage

- If any clinical trial protocol change, major CMC change or non-clinical research safety concern occurs during the clinical trial period, the applicant should timely report the change to the agency.

- Annual Report System
  - New toxicological, CMC or other study information.
  - Plans for subsequent studies, revision information, all changes, major global progress (eg. withdrawal from market, on-hold) etc.

Post-marketing Variation Management

- Technical Guideline of Post-Approval Variations for Biological Products (Draft for Comment)
- General Principles
  - Main responsibility : manufacturers or marketing authorization holders
  - Goal and regulatory compliance
  - Comparability study
  - Bundled changes
  - Design space: QbD
- Type of Changes
  - Type I: minor
  - Type II: moderate
  - Type III: major
- Applicants submit variations through supplementary application, record filing, or annual report according to Drug Registration Regulations and relevant requirements

Thanks!

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