Recent Trend in the Regulation of Biological Products in China

CMC Strategy Forum EU 2019

Suyuan CHENG
Division of Pharmaceutical Science of Biological Products
CDE,NMPA
Outline

• I. Background of Drug Regulatory Reform
• II. Work Mode under New Situation
• III. Regulations related to biological products
• IV. Application of biological products in 2018
• V. Key works of biological products in 2019
03/21/2018: SAMR Established

Merger of
- state administration for industry & commerce of the PRC
- General Administration of Quality Supervision of the PRC
- China Food and Drug Administration

Main Responsibilities
- Registration & Market Surveillance of Drugs, Medical Devices & Cosmetics
Divisions involved in biologics evaluation

- CMC division: Vaccine, Blood products, Tumor indications, Endocrine indications
- Pharmacology and toxicology division
- Clinical division
- Biostatistics division
Drug Regulatory Reform

Aims to enhance public health by establishing regulations to ensure the quality, efficacy, and safety of medical products

- Eliminate registration backlog and optimize procedures for IND/NDA approval
- Encourage drug innovation and improve the quality of medicines
- Optimize Regulations and promote Drug regulation legislation

Drug Regulatory Reform

- Eliminate registration backlog
- Encourage R&D
- Follow international standards

2017, Oct
Deepening Regulatory Reform Doc. No.42-2017

2017, Dec
Guideline for Conditional Approvals for Urgently Needed Drugs, draft

2018, Jan Notice No.10
Appling M4, E2A, E2D, M1, E2B Notice No.10-2018

2018, Jul Notice No.50
Adjust Review and Approval Procedures for CTA: 60 wd and pre-IND meeting

2018, Jul
Guideline for Acceptance of Overseas Clinical Data

2018, Nov
List of 48 Urgently Needed Overseas New Drugs

- DAL: Drug Administration Law
- DRR: Amendment to Drug Registration Regulation

* 2018.11 1st List of 48 Urgently Needed Overseas New Drugs
2019.3 2nd List of 30 Urgently Needed Overseas New Drugs
Outline

• I. Background of Drug Regulatory Reform
• II. Work Mode under New Situation
• III. Regulations related to biological products
• IV. Application of biological products in 2018
  - V. Key works of biological products in 2019
Drug review concept under new situation

• Base on the principle of justice, fairness and openness
• Implement the Concept of Scientific Review and Promote the Innovation of Supervision Work
• Built Clinical-oriented Benefit Risk Assessment and Risk Management Review System
• Implement Drug Life Cycle Management
Review system based on clinical efficacy evaluation

- **Review mode**
  - Guide in advance, communicate in the process, review decision-making in the last.

- **Review team**
  - Based on the claimed indication, which is led by clinical reviewers and composed of each discipline reviewers and project manager

- **Communication platform**
  - Communication between applicants and reviewers, Consultation on General Technical Questions, Expert consultant, Information disclosure
pre-IND/NDA consultation meeting

- Pre-IND meeting
- IND Application 60 wds
- Clinical Trial Phase I, II & III
- Pre-IND meeting 150 wds
- NDA application
- NDA approval by NMPA
In 2018, the application of consultation meeting were 1982 (up 136% year-on-year). 322 meetings were held, and the rest were answered in writing.

- Network platform consultation were 15219 times (up 159% year-on-year)
- Telephone consultation were 10,000 times,
- E-mail consultation were thousands of times.

Good communication improve the review quality and efficiency

Up to 2019.5.10，615 applications for clinical trials obtain Notice of Clinical Trails
Outline

• I. Background of Drug Regulatory Reform
• II. Work Mode under New Situation
• III. Regulations related to biological products
• IV. Application of biological products in 2018
• V. Key works of biological products in 2019
III. Regulations related to biological products

Laws:
- Drug Administration Law of the PRC (2015 amendment)
- Implementation Rules of the Drug Administration Law of the PRC

Many regulations including:
- Drug Registration Regulation

Two main types of guidance:
- Generally clarifications of policy - e.g.
- Technical standards.
All posted on NMPA’s website

Be noted that product quality needs to meet with those standards in Chinese Pharmacopeia
Guidelines related to biological products

• http://www.cde.org.cn/linshi/regulatEn/regulatMainEn.jsp
Recently drafted or published Guidelines

• Guidelines for the Study of Stability of Biological Products （Published, 2015.4）
• Guidelines for Research and Evaluation of Cell Products (Trial Version, 2017.12)
• Guidelines for Clinical Similarity Study and Evaluation of Vaccines (To be published)
• Guidelines for Post-marketing Change of Biological Products (For comments)
• Guidelines for the Application of Biomarkers in the Development of Antineoplastic Drugs (Drafting)
• Guidelines for phase IV clinical trials of vaccines (To be drafted)
Outline

• I. Background of Drug Regulatory Reform
• II. Work Mode under New Situation
• III. Regulations related to biological products
• IV. Application of biological products in 2018
• V. Key works of biological products in 2019
Acceptances of biological product review from 2016 to 2018 (annual task)

The total number of yearly accepted biological product applications is in the range of 400 to 900 over the past three years (by acceptance numbers). Due to the effort of resolving the backlog of drug review and approval, 2018 has seen a significantly progress in the number of applications completed. In 2018, the number of tasks completed is almost 1.5 times that of accepted tasks.

Note: Review completions means the review tasks which have completed by CDE and submitted to CFDA.
Biological product application in 2018

<table>
<thead>
<tr>
<th></th>
<th>Pending number</th>
<th>Product</th>
<th>Applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptance</td>
<td>923</td>
<td>257</td>
<td>296</td>
</tr>
</tbody>
</table>

Trends in the number of acceptance per month

![Bar chart showing trends in the number of acceptance per month]
Application for different kinds of biological products in 2018
Summary of Evaluation and Approval of Biological Products in 2018

According to the type of products:
- Vaccine: 229 (17%)
- Therapeutic biological products: 1129 (83%)

According to the type of application:
- IND: 499 (37%)
- BLA: 148 (11%)
- Supplementary And license renewal: 711 (52%)

Among all the applications, the supplementary applications are the most, accounting for about 50%, followed by the IND applications.
The numbers of IND applications and BLA increased stably these years.
Outline

• I. Background of Drug Regulatory Reform
• II. Work Mode under New Situation
• III. Regulations related to biological products
• IV. Application of biological products in 2018
• V. Key works of biological products in 2019
V. Key works of biological products in 2019

- Vaccine surveillance
- Innovative biological products
- Biosimilar
- ICH related
Vaccine surveillance

• To meet the requirements of capacity building of WHO National Regulatory Authority (NRA)

• Improve the guidelines system of vaccine
  – Draft Guidelines for Post-marketing Change of Production Process of Vaccine
  – Draft Guidelines for Classified Management of Vaccine

• Promote the upgrading of Vaccine Industrialization

• Priority review of innovative vaccines and vaccines urgently needed in clinic
Legislative process of vaccine law

• 2018.11.11  Law of the People's Republic of China on Vaccine Administration (draft for comments)

• 2018.12.23  The draft law on vaccine management was first submitted to the seventh meeting of the Standing Committee of the 13th National People's Congress for consideration.

• 2019.4.26  Law of the People's Republic of China on Vaccine Management (Revised draft for comments)

  – The second review draft of the Vaccine Law has revised the opinions on vaccine development and innovation incentives, urgently needed vaccine supply, vaccination management, and identification criteria of abnormal response to vaccination.
Key works of biological products in 2019

Innovative antibody

- New sequence antibodies (biobetter or new target antibodies)
- Bispecific antibodies (or antibody cocktails)
- Antibody drug conjugates (ADC)
## Innovative Mab

### PD-1/PD-L1 BLA Application in China

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date of NDA filing</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab Injection</td>
<td>2017/11/1</td>
<td>second-line NSCLC (Approved)</td>
</tr>
<tr>
<td>Pembrolizumab Injection</td>
<td>2018/2/11</td>
<td>Melanoma (Approved)</td>
</tr>
<tr>
<td>Teruipuli monoclonal antibody injection</td>
<td>2018/3/20</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Sintilimab injection</td>
<td>2018/4/19</td>
<td>Classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>Camrelizumab for Injection</td>
<td>2018/4/23</td>
<td>Classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>Tislelizumab injection</td>
<td>2018/9/4</td>
<td>Classical Hodgkin lymphoma</td>
</tr>
</tbody>
</table>
Consideration of Risk Control and Stage Requirements for Pharmaceutical Research in Clinical Development of Innovative Mab

- Innovation
- Clinical phase-appropriate
- Progressing
  - The first-in-human trial focuses on pharmaceutical issues affecting the safety
  - Early clinical development phase focuses on assessing whether changes introduce safety risks
  - Assessment of whether changes affect the safety and effectiveness of drug use in clinical trials at the late stage of clinical development
  - Ensure comparability of BLA and key clinical trials when applying for approval
Cell therapy

- Guideline on Pre-clinical Trial and Quality Control of Stem Cell Products Intended as Medicinal Technology, published jointly by CFDA and NHFPC in 2013.

  - Specifying the institute’s qualification, the clinical trial procedure, reporting system, experts committee, supervision, etc.

- Guideline for Research and Evaluation of Cell Therapeutic Products, published by CDE in 2017 (Trial Version)

- Key Points for Consideration of Quality Control and Detection of Cell Therapeutic Products and Non-clinical Research published by NIFDC in 2018.

Note: NHFPC, National Health and Family Planning Commission of the PRC
# CAR-T PhI Clinical Trials in China

<table>
<thead>
<tr>
<th>Target</th>
<th>Indication</th>
<th>Manufacturing Enterprise</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19</td>
<td>Diffuse large B cell lymphoma acute lymphoblastic leukemia</td>
<td>University of Pennsylvania, Novartis</td>
</tr>
<tr>
<td>CD19</td>
<td>B cell malignancies</td>
<td>Kite Pharma, National Cancer Institute</td>
</tr>
<tr>
<td>CD19</td>
<td>Chronic Lymphocytic Leukemia</td>
<td>Juno Therapeutics</td>
</tr>
<tr>
<td>EGFR</td>
<td>Glioblastoma</td>
<td>University of Pennsylvania, Novartis</td>
</tr>
<tr>
<td>BCMA</td>
<td>Multiple myeloma</td>
<td>University of Pennsylvania, Novartis</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>pleural mesothelioma, malignant mesothelioma, Breast cancer, Lung cancer</td>
<td>Memorial Sloan Kettering Cancer Center</td>
</tr>
<tr>
<td>HER2</td>
<td>sarcoma</td>
<td>Baylor College of Medicine, Texas Children's Hospital, The Methodist Hospital</td>
</tr>
<tr>
<td>mROR1,ROR1</td>
<td>Solid tumor, Blood cancer</td>
<td>Fred Hutchinson Cancer Research Center, Juno Therapeutics</td>
</tr>
<tr>
<td>PD-1,CD19</td>
<td>B cell lymphoma</td>
<td>Beijing Marino, Peking University</td>
</tr>
<tr>
<td>CD22</td>
<td>acute lymphoblastic leukemia</td>
<td>Cellectis</td>
</tr>
</tbody>
</table>
# CAR-T PhII Clinical Trials in China

<table>
<thead>
<tr>
<th>Target</th>
<th>Indication</th>
<th>Manufacturing Enterprise</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19</td>
<td>Acute lymphocytic leukemia, Non-hodgkin’s B lymphoma</td>
<td>Fred Hutchinson Cancer Research Center, Juno Therapeutics, Seattle Children’s Research Institute', Memorial Sloan Kettering Cancer Center, Celgene, TaKaRa Bio</td>
</tr>
<tr>
<td>CD19</td>
<td>B cell lymphoma, Leukemia</td>
<td>Bluebird bio, Celgene</td>
</tr>
<tr>
<td>CD19</td>
<td>Acute lymphocytic leukemia, Non-hodgkin’s lymphoma</td>
<td>Anke Bio</td>
</tr>
<tr>
<td>CD22,CD19,CD20</td>
<td>B cell lymphoma, Leukemia</td>
<td>Chinese PLA General Hospital</td>
</tr>
<tr>
<td>BCMA</td>
<td>Multiple myeloma</td>
<td>Nanjing Chuanqi, Janssen Biotech</td>
</tr>
<tr>
<td>BCMA</td>
<td>Acute lymphocytic leukemia, Non-hodgkin’s B lymphoma</td>
<td>Juno Therapeutics</td>
</tr>
<tr>
<td>EGFR</td>
<td>Glioblastoma</td>
<td>Kite Pharma, National Cancer Institute</td>
</tr>
<tr>
<td>EGFR</td>
<td>Colorectal cancer</td>
<td>Pregene Bio Pharma</td>
</tr>
<tr>
<td>HER2</td>
<td>Pleomorphic glioma</td>
<td>Aurora Bio Pharma</td>
</tr>
<tr>
<td>CD20</td>
<td>Non-hodgkin’s lymphoma</td>
<td>Fred Hutchinson Cancer Research Center, Mustang Bio</td>
</tr>
</tbody>
</table>
Key works of biological products in 2019

**Biosimilar**

- Similar not identical, biomedicinal similar
- Comparability study
- Original as reference
- Critical process control, Critical quality attributes similar
- Well designed and controlled Clinical trial, PD marker may be used as clinical surrogate endpoint
- Post market surveillance, immunogenicity
Biosimilar

• 2019.2.25  First biosimilar was approved by NMPA
  – Original : Rituximab (Roche)
  – Manufacturer: Fu Hung Han Lin
  – Package: 100mg/10ml/vial
  – Indication: Non-Hodgkin's lymphoma

• Several biosimilars are on BLA stage

• Dozens of biosimilars are on different clinical trial stage

• Guidelines for Research and Development and Evaluation of Biosimilars (Trial version) 2015.3
Key works of biological products in 2019

ICH guidelines related to biological products

• Establish ICH working group in CDE
• Participate in revision and improvement ICH guidelines
  – ICH Q5: Quality of Biotechnological Products
    • Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell lines of Human of Animal Origin
    • Q5B: Quality of Biotechnological products: Analysis of the Expression Construct in cells Used for Production of r-DNA Derived Protein Products
    • Q5C: Quality of Biotechnological products: Stability Testing of Biotechnological/biological Products
    • Q5D: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
    • Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process
Challenges

• Globalization: Global simultaneous development
• New technologies & New methods & New concepts
• ICH guidance alignment/Integration
• Post-marketing Supervision Management
• Drug Accessibility, encouraging development of biosimilars
Thank you!

chengsy@cde.org.cn