Overview of biological product evaluation in CDE, CFDA

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Outline

- Introduction of CDE and biological product review
- Changing undergoing in CDE
- Guidelines and hot topics concerning biologics
- New concept, practice & challenge
- Review of import biological product applications by CDE from 2014 to 2016
Part 1:
Introduction of CDE and biological product review
Organization Frame Diagram of CDE
Functions of CDE

Technical review of drug registration applications (IND/NDA/supplemental)

Other tasks assigned by CFDA

Guiding drug review activities of local authority

Involved in developing regulations, rules and policy

Following up application trend and legal issues related to drug evaluation

International collaboration and cooperation

Duties and Responsibilities
Divisions involved in biologics evaluation

- CMC division
- Pharmacology and toxicology division
- Clinical division
- Biostatistics division
Part 2: Changing undergoing in CDE
The Opinions of the State Council on Reforming the Evaluation and Approval System of Drugs and Medical Devices (No. 44[2015] of the State Council), —— issued by the State Council On Aug. 18, 2015, —— the milestone of China’s reform on Drug Evaluation and Approval system.
What’s said in the State Council’s document?

- To resolve the backlog of drug review and approval, to exercise strict control over the approval of oversupplied drugs.
- To optimize the review and approval procedures of innovative drugs.
- To adjust drug registration classification, defining the new drugs more stringently.
- To strengthen the clinical test verification.
- To carry out the pilot work of Drug Marketing Authorization Holder (MAH) System.
- Others: Service based on the mode of government purchase;
  - Quality consistency evaluation for generic drugs;
  - Simplified drug approval process;
  - Strengthened communication and information disclosure in review and approval.
Changing undergoing in CDE, CFDA

- Applicable guidelines issued by CFDA or other international agency
- Guidelines on phase I clinical trial (for comments and suggestion), with simplified data requirements for application dossier
- Application and designation for priority review, pre-IND meeting, and accelerated approval
- CMC Changes during development and/or post marketing, developing guidelines
Part 3: Guidelines and hot topics concerning biologics

- Biosimilars
- Recombinant Mab application and approval
- Innovative biologics
- Cellular therapy
I. Biosimilars

- Similar not identical, biomedical similar
- Comparability study
- Original as comparator
- 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
Diagram for Decision-making of Biosimilar Development

- **CMC and quality comparing study**
- **Non-clinical**
- **Clinical**

**Similar**
- PD, PK, immunogenicity

**Similar**
- PD, PK, immunogenicity

**Similar**
- Clinical pharmacology, safety and efficacy

**Difference**
- PD, PK, toxicity

**Difference**
- Clinical pharmacology, safety and efficacy

Uncertainty

**Not similar**

Biosimilar

Carefully going on

Better to quit

Better to quit

Better to quit
II. Recombinant Mab application and approval

- Antigen target or clinical indication
- Clinical trial approved
- Marketing application approved
- Application under review
List of Mab (hot target and indication)

- **Antigen target**
  - EGFR, IgE, TNF-α, IL-12, IL-6R, IL-8 DR5, RANKL, BlyS, CD20, VEGF, CD38, HER2, CD52, CTLA-4, LFA-3, CD-22, CD-11a, CD25, PD-1, PD-1L, IL-17A, IGF-1R and so on

- **Disease or indication**
  - Tumor, autoimmune disease, infectious disease, respiratory disease, cardiovascular disease, neuron disease, and so on
III. Innovative biologics

- Unmet medical needs
- Accelerated approval procedure, top priority review
- Pre-IND meeting and pivotal clinical trial meeting
- Guidance on phase I clinical trial application （for comments and suggestion）
- Conditional approval on market
- Committed study
IV. Cellular therapy

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

- Measures for the Administration of Clinical Trials for Stem Cell Products, issued by NHFPC in 2015.
  - Specifying the institute's qualification, the clinical trial procedure, reporting system, experts committee, supervision, etc.

- Drafting guidelines on cellular products intended for biologics registration, by CDE in 2016 (for public consideration).

Note: NHFPC, National Health and Family Planning Commission of the PRC
Part 4: New concept, practice & challenge
New concept & challenge
(Definition and understanding of “biosimilar”)

- Physical-chemical structure vs. biological function,
  apparently characteristic vs. substantial effect;
- Pharmaceutical attributes (product quality)
  vs. clinical therapeutic performance (clinical value);
- Local aspects of data vs. whole profile of product;
- Clinical evidence, totality.
New practice and challenge
(Continuous manufacturing and QbD)

- Batch or lot definition, quality consistency;
- Variation control; space design, validation;
- Manufacturing cycle, “holding”, in process control, PAT;
- Homogeneous, pooling & combining;
- Manufacturing capacity and matching between steps, seamless connection between upstream and downstream, and among process facilities or steps;
- Model separation and combination in system.
Part 5:
Review of import biological product applications (2014 ~ 2016)

• Application acceptances and review completions
• Comparison between import applications and domestic applications
• Priority review list
Acceptances and completions of biological product review from 2014 to 2016 (annual task)

Note: Review completions means the review tasks which have completed by the CDE and submitted to the CFDA.

The total number of yearly accepted biological product applications is in the range of 400 to 600 over the past three years (by acceptance numbers). Due to the effort of resolving the backlog of drug review and approval, 2016 has seen a significantly progress in the number of applications completed. In 2016, the number of tasks completed is 1.5 times that of accepted tasks.
Of the accepted tasks, vaccine tasks are less than therapeutic tasks.
It is the same with the tasks completed.
Comparison between import applications and domestic applications from 2014 to 2016

The number of import applications is comparable with domestic applications over 2014～2016.
The proportion of completed tasks to accepted tasks for import applications is comparable with that for domestic applications.
Comparison between import applications and domestic applications (vaccine vs. therapeutic product)

For vaccine review, domestic applications are more than import applications. Contrarily, the domestic applications are less than import applications for therapeutic product review.
Among the import applications of biological products, the supplementary applications are the most, accounting for more than 50%, followed by the IND applications. The numbers of IND applications and BLA increased stably these years.
### Biological products listed in priority review in 2016

<table>
<thead>
<tr>
<th>Acceptance number</th>
<th>Type</th>
<th>Name</th>
<th>Indications</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 JXSS14xxxx</td>
<td>BLA</td>
<td>Adalimumab Solution for Injection</td>
<td>Rheumatoid arthritis (RA)</td>
<td>Import application</td>
</tr>
<tr>
<td>2 JYSB14xxxx</td>
<td>Supplementary application</td>
<td>Insulin Glargine Injection</td>
<td>Diabetes type 1 and type 2</td>
<td>Approved</td>
</tr>
<tr>
<td>3 JYSB14xxxx</td>
<td></td>
<td>Note: the same product</td>
<td></td>
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<tr>
<td>4 JXSS16xxxx</td>
<td>BLA</td>
<td>Reassortant Rotavirus Vaccine, Live,Oral,Pentavalent(Vero Cell)</td>
<td>Prophylactic vaccine</td>
<td>Being reviewed</td>
</tr>
<tr>
<td>5 JXSS16xxxx</td>
<td>BLA</td>
<td>Tocilizumab Injection</td>
<td>Active systemic juvenile idiopathic arthritis(sJIA)</td>
<td>Approved</td>
</tr>
<tr>
<td>6 JXSS16xxxx</td>
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<td>Note: the same product with different specifications</td>
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<td>7 JXSS16xxxx</td>
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<tr>
<td>8 CXSL16xxxx</td>
<td>IND</td>
<td>Recombinant Human Coagulation Factor VIII for Injection</td>
<td>Hemophilia A</td>
<td>Domestic application Waiting for sponsor's reply</td>
</tr>
<tr>
<td>9 CXSL16xxxx</td>
<td>IND</td>
<td>Therapeutic Hepatitis B Adenovirus Injection</td>
<td>Chronic hepatitis B</td>
<td>Domestic application Waiting for sponsor's reply</td>
</tr>
<tr>
<td>10 JXSL16xxxx</td>
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<td>Import application   Waiting for sponsor's reply</td>
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Among 15 (by acceptance numbers) or 7 (by products) priority review tasks in 2016, only 2 are domestic applications.
Thank you
Back up slides
Acceptances and completions of biological product review from 2014 to 2016 (IND/BLA/Supplemental/re-registration)

The supplementary applications are the most, accounting for nearly 50% of all the applications, followed by the IND applications, then the BLA and the import re-registration applications.