China NMPA Drug Regulatory Framework Reform

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Agenda

• I. Organization
• II. Main Drug Regulations in China
• III. Drug Regulatory framework Reform
• IV. Challenges and Future Perspectives
I. Organization

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
I. Organization: SAMR

Main Responsibilities
-- Registration & Market Surveillance of Drugs, Medical Devices & Cosmetics

State Administration of Industry and Commerce
General Administration of Quality Supervision, Inspection and Quarantine
National Medical Product Administration (NMPA)
National Development and Reform Commission in respect of price supervision and anti-trust law enforcement
Ministry of Commerce in respect of antitrust law enforcement
Office of Anti-Trust Committee, State Council
State Intellectual Property Office
I. Organization: NMPA’s Affiliated Institutions

- **National Institutes for Drug Control**: National statutory Institutions and the highest technical arbitration body for drugs and biological products.

- **Chinese Pharmacopoeia Commission**: Organize Chinese Pharmacopoeia compilation, formulate and revise national Pharmaceutical standards as statutory national drug standard management agency.

- **Center for Drug Evaluation**: Responsible for technical review of drug registration application as NMPA Drug Registration technical review Agency.

- **National Committee on the Assessment of the Protected Traditional Chinese Medicinal Products**: Undertake national TCM protection and technical review of health food, cosmetics approval.

- **Center for Medical Device Evaluation**: Responsible for technical review of import medical devices and domestic Class III medical Devices.

- **Center for Complaints and Report**: Accept complaints for illegal activities in medicines, medical devices, health food and cosmetics in development, production, distribution, use and catering food service.

- **Center for Drug Reevaluation (National Center for ADR Monitoring)**: Responsible for conducting drug adverse reactions and medical device adverse events monitoring at home and abroad.

- **China Center for Food and Drug International Exchange**: Responsible for conducting international cooperation and exchange activities to serve administration of food, drugs, medical devices and cosmetics.

- **Center for Food and Drug Inspection**: Responsible for conducting quality system audit and unannounced inspection for drugs and medical devices.
II. Regulations

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
III. Drug Regulatory Reform

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

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

CFDA Joining ICH
2017, Jun

Adjustment of Imported Drug Registration
2017, Oct
Order No. 35

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

CFDA issued Chinese Orange Book
2017, Dec

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

Guideline for Acceptance of Overseas Clinical Data
2018, Jul

List of 48 Urgently Needed Overseas New Drugs
2018, Aug

Adjust Review and Approval Procedures for CTA: 60 wd and pre-IND meeting
2018, Jan
Notice No.10

Appling M4, E2A, E2D, M1, E2B Notice No.10-2018
2018, Jul
Notice No.50

Guideline for Acceptance of Overseas Clinical Data
2018, Jul

List of 48 Urgently Needed Overseas New Drugs
2018, Aug

Objectives

- Eliminate registration backlog
- Encourage R&D
- Follow international standards
III. Drug Regulatory Reform: Clearing Backlog

Creating an efficient process to clear the severe registration backlog of drug applications

- roughly form 2015 to the end of 2017
- increased the drug registration fee
- mandated self-examination and inspection of clinical data
- identification of redundant generic applications
- rejection of deficient applications
III. Drug Regulatory Reform: Encouraging Innovation

Encouraging innovation
- MAH (Doc. 44 & 42)
- Approval process acceleration
- Clinical trial management
- Lifecycle management
- Intellectual property protection: exploring a drug patent linkage system, initiating a patent term restoration pilot programme, implementing a clinical trial data protection system
- China’s joining the International Conference on Harmonization
III. Drug Regulatory Reform: Hotspots of 2018

• Optimize procedures for IND/NDA approval
• Acceptance of overseas clinical trial data
• Conditional approval
• Change management based on risk assessment
• Breakthrough therapy and advanced therapy in China
• ICH guidance alignment/Integration : CFDA decided to apply five ICH Secondary Guidelines: M4, E2A, E2D, M1, E2B(R3)
III. Drug Regulatory Reform: Hotspots of 2018

Optimize the Procedures for IND/NDA Approval

- 60 working days for the approval timelines of IND, 150wds for NDA
- Ph 1 trial is allowed in China to enable China joining global simultaneous development
- Review based registration test and inspection
- One CTA approval is valid for Phase I, II and III trials
- CHANGE MANAGEMENT based on risk assessment
- A linked review and approval regime (similar to US DMF) for API, excipients and packaging materials with DP application together
NDA/BLA Process for Import Products

Notes:
The steps outlined by dotted line maybe skipped
1 Testing: in parallel to CDE review, 3 batches of DS & DP samples for biologics
2 CDE question release after review finished and QC testing report transferred to CDE
3 F2F hearing meeting: arranged by CDE if CDE has inquires and need F2F tripartite communication with applicant and CDE external experts
4 Pre-approval GCP inspection required since Jul 2015, focus on authenticity of data
5 Assuming QC testing and GCP inspection are not critical path
III. Drug Regulatory Reform: Hotspots

pre-IND/NDA consultation meeting
III. Drug Regulatory Reform: Hotspots

Accelerate Review and Approval of Drugs In Urgent Medical Needs

- Implement the priority review and approval: AIDS, Tuberculosis, Viral hepatitis, Rare disease, Malignant tumor, Pediatric, Diseases with high incidence or unique in elderly people

- Conditional Approval to Meet the Medical Need, e.g., orphan drugs, innovative drugs targeting life threatening diseases without effective therapies

- CPP is no longer required for NDA submission: would shorten China approval gap with US/EU.
III. Drug Regulatory Reform: Hotspots

Guidelines for Acceptance of Overseas Clinical Trial Data

Foreign data can be accepted if the data package meets China’s regulatory requirements:

For Approved overseas orphan drugs and those drugs which are effective in treating life threatening diseases without any current available treatment in China, sponsors could submit NDA applications directly (they needn’t first submit an IND application), if it has been proven to be effective among all races and ethnic groups. This process is Not suitable for vaccines.

For an NDA registration of drugs being developed Globally Simultaneously, sponsors should submit an unabridged clinical trial data package that contains all of the clinical trial data obtained from all regions, both in china and overseas.

Changes management based on risk assessment
- CFDA published Guideline for Site Changes to An Approved NDA/ANDA (draft for comments)
III. Drug Regulatory Reform: Hotspots

ICH guidance alignment/Integration

- CFDA held several meetings and seminars to discuss the applicability of ICH guidelines, find controversial articles, by comparing CHINA’s current drug regulations, Chinese pharmacopeia and guidelines.

- CFDA decided to apply five ICH secondary guidelines, namely M4, E2A, E2D, M1, E2B(R3)

- We encourage applicants to submit their application dossier in CTD form, in addition we held many lectures about M4

- We invited foreign pharmaceutical companies, to introduce Q12, as it is related to QbD, and continuous manufacture
### III. Drug Regulatory Reform: Hotspots

**PD-1/PD-L1 NDA Application in China**

<table>
<thead>
<tr>
<th>Enterprise</th>
<th>Drug</th>
<th>Date of NDA filing</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>Nivolumab Injection</td>
<td>2017/11/1</td>
<td>second-line NSCLC (Approved)</td>
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<tr>
<td>Merck &amp; Co., Inc</td>
<td>Pembrolizumab Injection</td>
<td>2018/2/11</td>
<td>Melanoma (Approved)</td>
</tr>
<tr>
<td>TopAlliance Biosciences Inc.</td>
<td>Teruipuli monoclonal antibody injection</td>
<td>2018/3/20</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Innovent Biologics, Inc.</td>
<td>Sintilimab injection</td>
<td>2018/4/19</td>
<td>Classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>Beigene Ltd.</td>
<td>Tislelizumab injection</td>
<td>2018/9/4</td>
<td>Classical Hodgkin lymphoma</td>
</tr>
</tbody>
</table>
III. Drug Regulatory Reform: Hotspots

CAR-T CMC Requirements

- CAR design: costimulatory domains, scFv affinity
- Quality of T cells: T cell subsets, vectors, culture conditions
- Host Specific Factors: TME, ICMs, Tumor heterogeneity
- Quality Control:
  - plasmid: DNA sequencing, concentration, DNA homogeneity, HOST CHROMOSOMAL DNA, host RNA, host protein, residual antibiotics
  - virus vector: CAR gene identify, host DNA, host protein, BSA, size distribution of residual DNA, viral titer
  - CAR-T: CAR expression, cell viability, CAR+T cells, CD3+ T cells, residual beads, in vitro IFN-gamma secretion, sterility, replication competent lentivirus
IV. Challenges

- Globalization: Global simultaneous development
- New technologies & new methods
- ICH guidance alignment/Integration
- Drug life cycle management, e.g., drug withdrawal system building
- Drug Accessibility, encouraging development of biosimilars
IV. Future Perspectives

- Reviewer pertaining and continuous training
- Information system building
- Regulatory science
Thanks!