Comparison of US vs China’s Regulatory System

Dan Zhang (张丹) MD, MPH
2018年5月3日
## Regulatory System: three years ago

<table>
<thead>
<tr>
<th>IND</th>
<th>Clinical Trial</th>
<th>NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration: 12-24 Month</td>
<td>Only conducted in 600+ GCP centers</td>
<td>“three application &amp; three approvals” for imported drug</td>
</tr>
<tr>
<td></td>
<td>Foreign firms can not conduct first-in-man trial</td>
<td>No foreign data accepted</td>
</tr>
<tr>
<td></td>
<td>Totally different Safety handling system</td>
<td>No CMO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manufacturer must be in China if applying NDA first</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No 505 b(2) policy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No clear orphan policy</td>
</tr>
</tbody>
</table>
### What Happened in Last Three Years

<table>
<thead>
<tr>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>State Council Document 44:</strong></td>
<td><strong>New Drug Definition and Classification System</strong></td>
<td><strong>Become a ICH member</strong></td>
</tr>
</tbody>
</table>
| - Eliminated all MA backlogs via voluntary withdrawal | - Global New Implications:  
  - Must file CN NDA before MA approval anywhere else  
  - Include Chinese sites in global trials | - Initiate FIH trial & get first approval in China! |
| - Established Green Channel | - Required BE for all generics | - Central Party Office & State Council (Oct 8): Doc #42  
  - 36 proposals  
  - Summary of 2 year effort  
  - 19th National Party Conference  
    - Unsatisfied demand  
    - Demand for better Care |

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New policies issued in 2017

- 《关于鼓励药品医疗器械创新加快新药医疗器械上市审评审批的相关政策》（征求意见稿）意见的公告（2017年第52号）
  • Speed-up review process

- 《关于鼓励药品医疗器械创新改革临床试验管理的相关政策》（征求意见稿）意见的公告（2017年第53号）
  • Reform the process for conducting clinical trials in China

- 《关于鼓励药品医疗器械创新实施药品医疗器械全生命周期管理的相关政策》（征求意见稿）意见的公告（2017年第54号）
  • Life-Cycle Management of pharmaceutical and device products

- 《关于鼓励药品医疗器械创新保护创新者权益的相关政策（征求意见稿）》意见的公告（2017年第55号）
  • Patent Protection Policies (Similar to Hutch-Waxman Act)
CFDA Drug Application & Review in Year 2017
In year 2017, total of 394 NDAs were granted:

1) Chemical products: 369
2) Herbal products: 2
3) Biologics: 23
4) Domestic: 278 (NCE: 28; new herbal: 1; new biologics: 10; ANDA: 238)
5) Imported: 116
6) Priority review: 53 (13.5%)
In Year 2017, CDE completed 8773 reviews:

Backlog reduced from 22000 (Sept 2015) to 4000 （Dec 2017）
一、Applications and Reviews in Year 2017

Fig. 1  Changes of backlogs from year 2014-2017
Chemical Products: 7729 (88%)

Fig. 2 completed reviews among different class of products in year 2017,
一、Applications and Reviews in Year 2017

CDE Reviewed:

IND: 908 cases,
NDA 294 cases,
ANDA 4152 cases

Note: The number of varieties of chemical drugs is based on the statistical analysis of active ingredients. The number of varieties of Chinese medicine and biological products are reported under the generic names of drugs.
一、Applications and Reviews in Year 2017

（二）Application & reviews for Chemical Products

01 Overall Performance

Total: 7729, including ANDA 4135 (53%)

Fig. 4 Reviews for chemical products for year 2017
Decline in registration processing time:

1) BE/PK for Generic Product: 70 working days on average

2) The first round of IND review time is about 120 working days
Applications and Reviews in Year 2017

Figure 5 2012-2017 average IND review time
一、Applications and Reviews in Year 2017

Figure 6 2012-2017 average NDA review time
Applications and Reviews in Year 2017

Figure 7 2012-2017 ANDA review time
# Applications and Reviews in Year 2017

## 03 Applications’ Review results

### Table 1 2017 the approval status of chemical drugs registration applications

<table>
<thead>
<tr>
<th>申请类型</th>
<th>Approval Status (cases)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Approve</td>
<td>Not approve</td>
<td>Others</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>IND</td>
<td>481</td>
<td>7</td>
<td>54</td>
<td>542</td>
<td></td>
</tr>
<tr>
<td>Confirmatory clinical trial</td>
<td>419</td>
<td>92</td>
<td>85</td>
<td>596</td>
<td></td>
</tr>
<tr>
<td>NDA</td>
<td>113</td>
<td>35</td>
<td>88</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td>ANDA</td>
<td>272</td>
<td>1487</td>
<td>2376</td>
<td>4135</td>
<td></td>
</tr>
<tr>
<td>Supplementary application</td>
<td>1366</td>
<td>187</td>
<td>222</td>
<td>1775</td>
<td></td>
</tr>
<tr>
<td>Import re-registration</td>
<td>171</td>
<td>17</td>
<td>49</td>
<td>237</td>
<td></td>
</tr>
<tr>
<td>BE study</td>
<td>/</td>
<td>/</td>
<td></td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Review</td>
<td>/</td>
<td>/</td>
<td></td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>/</td>
<td>/</td>
<td></td>
<td>7729</td>
<td></td>
</tr>
</tbody>
</table>

Note: “Others” refer to voluntarily withdrawal application, waiting for the applicant to submit supplement information, and the non-CDE application submitted to the Food and Drug Administration of Drug Registration Division, Medical device registration Division for drug-device combination registration and the registration of raw materials/accessories withdrawal.
The CDE completed the review of 542 chemical drug IND, and approved 481 of them, 399 of which were new drug IND (170 chemicals). The total number of new drug IND approved doubled that of 2016.

Figure 8 The number of chemical drug IND approved from 2014 to 2017

Note: The application for the registration of chemotherapeutic drugs is reported in accordance with the requirements of Annex 2 to the “Administrative Measures for Drug Registration” (formerly the State Food and Drug Administration Order No. 28). Application for Registration of Chemicals Category 1.1 and in accordance with the requirements of Annex 1 of the “Notice on Announcement of Work Program for the Registration of Chemical Drug Registration Reform” (No. 51 of 2016). The application for registration of chemical class 1 declared is a global new drug that is not listed on the domestic and overseas markets.
Of the 170 IND approved by CDE, oncology drugs, digestive drugs, endocrine drugs accounts for 65%.

Figure 9 Pie chart of approved chemical drug IND in 2017
Biologics applications and reviews

Overview

- Completed, 678 in total
- IND
  - Preventive 63
  - Treatment 242
- NDA
  - Preventive 15
  - Treatment 35

Figure 12, Biologics reviewed in 2017
## Applications and Reviews in Year 2017

### Review results

- **Approved**
  - IND: preventive 40; treatment 187
  - NDA: preventive 8, treatment 21

Table 3, Review results of biologics in 2017

<table>
<thead>
<tr>
<th>Application Types</th>
<th>Approval Status (cases)</th>
<th>Approve</th>
<th>Not approve</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preventive-IND</strong></td>
<td></td>
<td>40</td>
<td>3</td>
<td>19</td>
<td>62</td>
</tr>
<tr>
<td><strong>Treatment- IND</strong></td>
<td></td>
<td>187</td>
<td>12</td>
<td>43</td>
<td>242</td>
</tr>
<tr>
<td><strong>Preventive-NDA</strong></td>
<td></td>
<td>8</td>
<td>4</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td><strong>Treatment-NDA</strong></td>
<td></td>
<td>21</td>
<td>0</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td><strong>Supplement</strong></td>
<td></td>
<td>218</td>
<td>11</td>
<td>59</td>
<td>288</td>
</tr>
<tr>
<td><strong>Import re-registration</strong></td>
<td></td>
<td>25</td>
<td>0</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td><strong>review</strong></td>
<td></td>
<td>/</td>
<td>/</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td><strong>合计</strong></td>
<td></td>
<td>/</td>
<td>/</td>
<td></td>
<td>678</td>
</tr>
</tbody>
</table>
CDE approved 227 biologics IND application.

Figure 13 Pie chart of biologic IND approved in 2017
二、Application accepted

（一）Overall status

01 Overview

- Total application in 2017--4837
  - Review needed 3783
    - BE 71
  - Review not needed 1054
  - Chemical drug
    - 3870
    - 80%
  - Herbals
    - 335
  - Biologics
    - 632

Figure 14, Pie chart of application received in 2017
二、Application accepted

02 Domestic application

- Type I application 402 (181 chemicals)
  - IND 379 (171 chemicals)
  - NDA 23 (10 chemicals)

- Chemical 324 (112 chemicals)
- Herbals 2 (1 chemicals)
- Biologics 76 (68 chemicals)

- Oncology, Infectious Diseases

03 Imported drug application

- Imported drug application 259 (133 chemicals)
  - 5.1 type new drug 117 (70 chemicals)
  - Type I new drug 75 (37 chemicals)
  - MRCT 67 (26 chemicals)

- Oncology, Infectious Diseases
Chemical drugs application

1. Overview

- Total application received 3870
  - IND 480
  - NDA 75
  - ANDA 548

Figure 15 Pie chart of chemical drug application received in 2017
New drug application

- Total new drug application 149
  - 66% increase compare to 2016
  - Domestic 112
  - Import: 37

Fig. 16  Chemical Products 2014-2017
# USA vs. China: Regulatory Asymmetry

<table>
<thead>
<tr>
<th></th>
<th><strong>USA</strong></th>
<th><strong>China</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td>30 days</td>
<td>more (60 wds)</td>
</tr>
<tr>
<td>IRB</td>
<td>Local &amp; central</td>
<td>Local Only</td>
</tr>
<tr>
<td>FIH</td>
<td>Anywhere</td>
<td>China only; now ICH E17</td>
</tr>
<tr>
<td>Global data</td>
<td>accepted</td>
<td>not before Oct 10</td>
</tr>
<tr>
<td>CMC</td>
<td>accepted</td>
<td>China only if NDA first</td>
</tr>
<tr>
<td>NDA</td>
<td>two pivotals</td>
<td>one</td>
</tr>
<tr>
<td>Orphan Policy</td>
<td>Yes</td>
<td>Murkey</td>
</tr>
<tr>
<td>User Fee</td>
<td>Yes</td>
<td>No, but more charges</td>
</tr>
<tr>
<td>Speedy Action</td>
<td>Yes</td>
<td>Yes, but different</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>immediately</td>
<td>2-3 years later</td>
</tr>
</tbody>
</table>
## USA vs. China: conducting clinical trials

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol Design</strong></td>
<td>Abundant</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>PI</strong></td>
<td>more, experienced</td>
<td>less, less experienced</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>Any place</td>
<td>GCP sites (600+)</td>
</tr>
<tr>
<td><strong>IRB</strong></td>
<td>Local &amp; Central</td>
<td>Local Only</td>
</tr>
<tr>
<td><strong>Genome Protection</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>HIPPA</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Patient Number</strong></td>
<td>Less than trial needed</td>
<td>Largest</td>
</tr>
<tr>
<td><strong>Patient Quality</strong></td>
<td>Less treatment naïve</td>
<td>Treatment naïve</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>High</td>
<td>1/3~1/4 US cost</td>
</tr>
<tr>
<td><strong>Quality for MRCT</strong></td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td><strong>Quality for Local trial</strong></td>
<td>Good</td>
<td>Very Poor</td>
</tr>
<tr>
<td><strong>CRO availability</strong></td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td><strong>CRO sophistication</strong></td>
<td>Excellent</td>
<td>Most are inadequate</td>
</tr>
</tbody>
</table>
What happened in 2018?

- **New Management System**
  - CFDA becomes a sub-unit of the Bureau of Market Supervision and Management (BMSM)
    - New head of CFDA: Ms. Hong Jiao, former deputy commissioner of CFDA in charge of medical devices
    - Former commissioner of CFDA (Mr. Bi): second-man in charge of the BMSM
  - Implications:
    - How about the implementation of policies already announced?
    - Content & speed?
    - Regional and local CFDA
    - Unsettled: cell-therapies

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What happened in 2018?

• Implementation of ICH
  – E17 MRCT (multi-region clinical trial)
    • First one since CFDA became a member of ICH
    • CFDA offered training in Beijing
  – M4 CTD
    • Implemented from Feb 1, 2018
    • eCTD?
  – ICH (E2 & M1) Safety Guidelines
    • Be implemented on May 1 (IND studies) & July 1 for marketed products
    • Shocking to domestic firms: lack of experienced team and infrastructures
    • Training is underway

• Chinese version of Hutch & Waxman Act
  – Patent Linkage & Compensation, data exclusivity
What happened in 2018?

• Importation tax is eliminated for oncology product
• New drug will be considered to add to insurance coverage
• Pricing is to be negotiated for entering into medical centers
• Super-fast approval for the Merck’s HPV Vaccine
  – NDA approval is granted within 4 days’ application
  – But IND took 2 years
  – It took 10 years for GSK HPV vaccine entering into China Market
ICH-Impact on Domestic Firms (I)

• Companies with promising future
  – With global-new, 505 B(2), or orphan indication products
  – With strong global BD capabilities
  – With well-established sales channel

• Bottleneck-experience GCP centers
  – Where are they located?
  – Who are they?
    • Clinical Development
    • Clinical Operation
    • DM/Biostat
    • Regulatory
    • Pharmacovigilance

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ICH-Impact on Domestic Firms （II）

• Fund-Raising in China
  – Hot for right companies with right products

• Going global by domestic firms
  – Survival techniques in the Era of ICH
    • Reimbursement Consideration
    • Return on Investment Consideration
  – IPO in USA or in Hong Kong

• More trans-border deals ($1.4 B Q1 2018)
  – JP Morgan conference
  – DIA China annual conference
  – ASCO conference
Impact on US biopharmaceutical Firms (I)

- Acceptance of clinical data generated outside of China
  - Immediately speed up IND/NDA process
  - Conditional acceptance of clinical data
    - Bridging trial: genetic variation?
    - Proper design of the trial: selection of active control-standard of care issue
    - Consider ICHE17 MRCT guidelines
  - ANDA for generics
    - Accept PK/BE data from ICH countries
  - Conditional approvals:
    - Orphan indications & unmed medical need
  - Compassionate use: possible now in China
- CMC information generated outside of China
  - No CPP is needed for the NDA application in China
  - MAH is possible
- Pre-clinical information generated outside of China
  - Yes if comes from qualified vendors or team
- CFDA reserves the right to conduct inspection
Impact on US biopharmaceutical Firms (II)

• Access to the largest patient population
  – Treatment Naïve Population
  – High Enrollment speed with low per-patient cost
  – Special patient population
  – Acceptance of clinical data from China for NDA in US
    • COMMIT Trial

• US-China simultaneous NDA application?
  – New drug definition in China: global new; patent issue
  – ICH E17 MRCT guideline
    • CDP planning
    • For ongoing phase III trials
Impact on US biopharmaceutical Firms (III)

• Patent Consideration in China
  – Patent Linkage & Compensation
  – Data Exclusivity

• Fund Raising
  – China vs global

• Multiple Exit Venues
  – IPO in US vs in Hong Kong
  – Global M&A: buyer from China

• New business model
  – IP+VC+CRO
  – Consider US & China as a unified market
Looking Forward

• More hiring by CDE of CFDA
  – 1200 reviewers as the target
  – More trainings

• More ICH guidelines will be implemented
  – Meeting with CDE of CFDA: need meeting minutes

• Implementation of eCTD

• More cautious approach by CFDA in short-run
  – Personnel changes

• Read the Document #42 issued on Oct 8, 2017

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GEOGRAPHICAL COVERAGE

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Thanks!

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