Recent Regulatory Changes in China and Impacts to the Clinical Trials from CRO Standpoint
China New Regulatory
New Drug Approval System Reform

The State Council 08Oct2017

Encourage Innovations and Genetic Drugs

- **Generic drug** consistency evaluation
- **MAH** (Marketing Authorization Holder) System
- **NDA** in parallel with other countries **without CPP**

**Optimize Clinical Trial Process**

<table>
<thead>
<tr>
<th></th>
<th>In the Past</th>
<th>New Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IND</strong></td>
<td>8-12 months</td>
<td>60 Working Day notice period.</td>
</tr>
<tr>
<td><strong>Phase 1</strong></td>
<td>Only after foreign region has phase 1 data.</td>
<td>Parallel early phase in China</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Clean the IND/NDA backlog by quality inspections.</td>
<td>Legal actions against fake data</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>GCP site accreditation</td>
<td>Online Registration (Future)</td>
</tr>
<tr>
<td><strong>IEC</strong></td>
<td>Each site has its EC.</td>
<td>Regional EC / Central EC (Future)</td>
</tr>
</tbody>
</table>

**Accelerate new Drug Approval**

<table>
<thead>
<tr>
<th></th>
<th>In the Past</th>
<th>New Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet urgent need</td>
<td>NA</td>
<td>Conditional approval on early clinical evidence</td>
</tr>
<tr>
<td>Rare Disease</td>
<td>NA</td>
<td>Issue China rare disease list, priority review and approval</td>
</tr>
<tr>
<td>Approval on Foreign Data</td>
<td>China study for NDA registration purpose.</td>
<td>Guideline on MRCT data acceptance, NDA approval based on MRCT result.</td>
</tr>
</tbody>
</table>

**MAH**: Marketing Authorization Holder
**CPP**: Certificate of a pharmaceutical product.

© 2018 All rights reserved | Confidential | For Syneos Health™ use only
Clear IND/NDA Backlog and Inspection on Quality

CFDA reducing backlog
From 22,000 cases (mid-Year 2015) to 4,000 (Year 2017)

Inspection on Quality
• 22Jul2015: CFDA announced to have on site inspections
• Two years after till Jul2017
  • 65% application withdrawn by sponsor
  • Finished inspections on 313 NDA applications
  • 185 inspection team (1635 person-time)
  • 763 site-time
Legal Actions Against Clinical Trial and Marketed

• Legal actions in case of fraudulent activities (Year 2015-2017 Summary)
  • Finished inspections on 313 NDA applications
  • 38 NDA may have the fake data, 30 NDA were rejected
  • Legal actions against to 11 sites and CROs

• China sacked top officials over vaccine scandal (Jul-Aug 2018)
  – 252,600 doses DPT (diphtheria, whooping cough and tetanus), plus rabies vaccine couldn’t meet the standard of immunity results
  – 18 suspects were detained
  – 7 senior government officials were punished
    • Bi Jingquan, former CFDA head resigned
    • Wu Zhen, one NMPA former deputy head, was investigated on anti-corruption
    • Two deputy governors of Jilin Province were dismissed or resigned
More and quicker Innovation IND Approvals

- Encourage China innovative drug to be developed in parallel with other global countries
- Number of chemical innovation IND approvals increased to 170 in 2017
- The average IND first-round review timeline was 120 working days
- The average priority IND first-round review timeline was 39 working days
- CDE consultation meetings for pre-IND, IND, phase 1, phase 2 and pre-NDA

**Chemical Innovation China IND Approval**

- Innovation: New medicine that was never approved globally.

**CDE Consultation Meeting**
Accelerate New Drug Availability

Global Data for China NDA

Gardasil 9
8 days, global data only
20 Apr 2018: NDA Applied
28 Apr 2018: Conditional approval for female 16-26 age

Based On:
• Global clinical data
• Some East Asia data
• Monitoring China subjects post-marketing.

In the Past

Cervarix
10 years to enter China
Jul 2016: China approval

Urgent Unmet Need & Rare Diseases

Oncology Medicine NDA Approval closely after US-FDA
15 Jun 2018: Nivolumab
25 Jul 2018: Pembrolizumab

Rare Diseases
11 May 2018: China published its Rare Disease List

Accelerate NDA Approval:
• Priority Review for “Breakthrough”
• Conditional approval
• Pre-IND / ongoing CDE meeting

Early Accessible prior to NDA Approval

Special approval at Hainan “Super-Hospital”
• New FDA-approved drug could be accessible even before China NMPA approval
• New medical device can be approved by Hainan province. (Normally approved by NMPA)

https://mp.weixin.qq.com/s/CzO3_1yPgx52MpLMRlZUA
New Policy Impact on China Market
China Market Change Overview

Affordable Medical Coverage

**Innovation**
- Optimize Clinical Trial Process
- First-in-man trial in China
- Global data for registration in China

**Genetic Drug**
- Generic drug consistency evaluation
- Price sensitive with large volume

---

**CRO View Point**

**Increasing Need**
- High quality at global standard
- First-in-class: will be in the future
- Me-too / Me-better are very competitive now

**Decreasing Need**
- Few China-only registration trial

---

**Increasing Need**
- BE (Bioequivalence) study
- Matthew effect (The strong pharm got stronger)

**Decreasing Need**
- Hard time to low level and poor quality pharms
New Policy Impacts on China Market

• Encourage the **first-in-class** drug development in China, parallel to US/EU
  – Shorten start up timeline and process in China (best scenario 7-8 months)
  – Encourage Phase I in China in parallel with globe
  – Pre-IND meeting with CDE to minimize the clinical development risks

• **Me-too / Me-better** will be much competitive

• Better quality with global **ICH** standard

• **Generic drug** bioequivalence is on the fast track

• To provide the affordable medical insurance coverage
China Innovative INDs among 170 Indications

The graph only includes those innovation medicines which are never approved globally

- Oncology (72 cases, 42%)
- Digestive (26 cases, 15%)
- Endocrinology (12 cases, 7%)

- PD-1 and PD-L1 are the hottest developing area
- Me-too or Me-better from China base global ambition companies
PD-1 / PD-L1 Landscape in China

PD-1 / PD-L1 Key Players:
- Global pharms lead the market.
- Four leading China-based pharms closely follow-up
- 20+ companies, highly competitive.

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>PD-1 / PD-L</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>Nivolumab (Opdivo)</td>
<td>PD-1</td>
<td>Marketing</td>
</tr>
<tr>
<td>MSD</td>
<td>Pembrolizumab (Keytruda)</td>
<td>PD-1</td>
<td>Marketing</td>
</tr>
<tr>
<td>Shanghai Junshi (君实)</td>
<td>JS001</td>
<td>PD-1</td>
<td>NDA</td>
</tr>
<tr>
<td>Heng Rui (恒瑞)</td>
<td>SHR-1210</td>
<td>PD-1</td>
<td>NDA</td>
</tr>
<tr>
<td>Innoven (信达)</td>
<td>IBI308</td>
<td>PD-1</td>
<td>NDA</td>
</tr>
<tr>
<td>BeiGene (百济)</td>
<td>BGB-A317</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>Roche</td>
<td>Atezolizumab (Tecentriq)</td>
<td>PD-L1</td>
<td></td>
</tr>
<tr>
<td>Merck/Pfizer</td>
<td>Avelumab (Bavencio)</td>
<td>PD-L1</td>
<td></td>
</tr>
<tr>
<td>AZ</td>
<td>Durvalumab (Imfinzi)</td>
<td>PD-L1</td>
<td></td>
</tr>
<tr>
<td>Alphamab</td>
<td>KN035</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>Gloria</td>
<td>GLS-010</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>CSTone</td>
<td>CS1001</td>
<td>PD-L1</td>
<td></td>
</tr>
<tr>
<td>HengRui</td>
<td>SHR-1316</td>
<td>PD-L1</td>
<td></td>
</tr>
<tr>
<td>Bio-Thera</td>
<td>BAT1306</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>Akesobio</td>
<td>AK103</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>Kelun</td>
<td>KL-A167</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>Livzon</td>
<td>LZM009</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>CHIATAI TianQing</td>
<td>TQB2450</td>
<td>PD-L1</td>
<td></td>
</tr>
<tr>
<td>Lee’s Pharm</td>
<td>ZKAB001</td>
<td>PD-L1</td>
<td></td>
</tr>
<tr>
<td>Henlius</td>
<td>HLX10</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>CSTone</td>
<td>CS1003</td>
<td>PD-1</td>
<td></td>
</tr>
<tr>
<td>Henlius</td>
<td>HLX20</td>
<td>PD-L1</td>
<td></td>
</tr>
</tbody>
</table>

Marketing Approval in China:
- 15 Jun 2018: Nivolumab (Opdivo, BMS) for lung cancer
- 25 Jul 2018: Pembrolizumab (Keytruda, MSD) for local advanced or metastatic melanoma.

PD-1 / PD-L1 Cancer Trials in China:

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Esophagus Cancer</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-Cell / NK-Cell Cancer</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urothelium Cancer</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td></td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC</td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Cancer</td>
<td></td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharynx Cancer</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A, B, C, D, E are different companies.
Generic Drug Consistency Evaluation

289 Categories listed by NMPA
Need to finish BE studies by end-2018
Only 13 past by Sep

Around 60 Sites can take BE trials
Site resources are limited

Clinical Cost
RMB 4-6 million (JPY 65-98 million) per trial

| Generic Medication Overview | Eliminate backward production capacity | Procurement quantity with low price | Matthew effect |
Overview
China Market Future View

Trial Landscape

- Build phase 1 centers of excellence
- Chinese KOLs have more access to membership of steering committees in global trials
- Global development strategy to include China from the very beginning.

China Site
- Better Trial infrastructures
- Upskill of site staff
- New clinical trial sites

Patients
- More innovative trial
- More patient education
- More Data sharing

Operational Readiness
- Skilled professional staff
- Resourced requirement for clinical staff
- Global standards