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

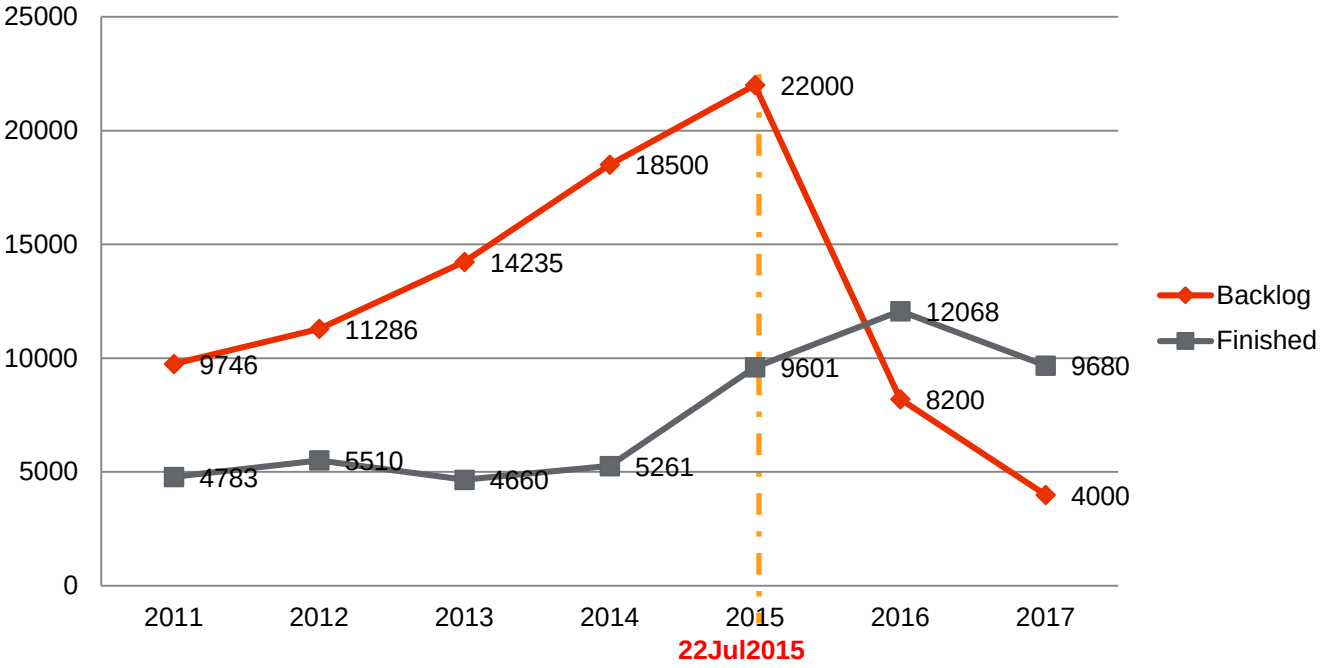
	In the Past	New Policy
IND	8-12 months	60 Working Day notice period.
Phase 1	Only after foreign region has phase 1 data.	Parallel early phase in China
Quality	Clean the IND/NDA backlog by quality inspections.	Legal actions against fake data
Site	GCP site accreditation	Online Registration (Future)
IEC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

Accelerate new Drug Approval

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

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

Clear IND/NDA Backlog and Inspection on Quality

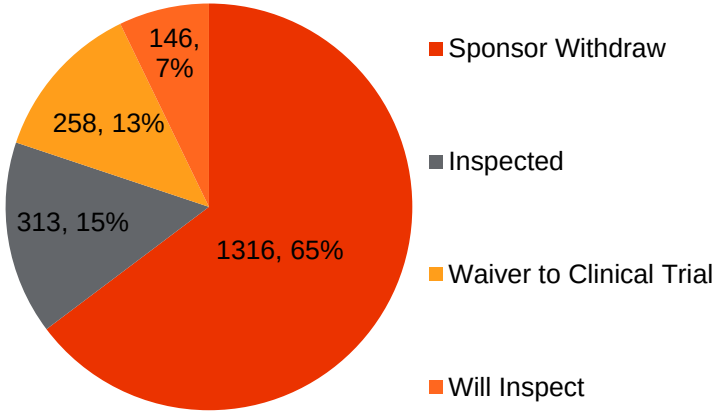


CFDA reducing backlog

From 22,000 cases (mid-Year2015) 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  - 65% application withdrawn by sponsor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

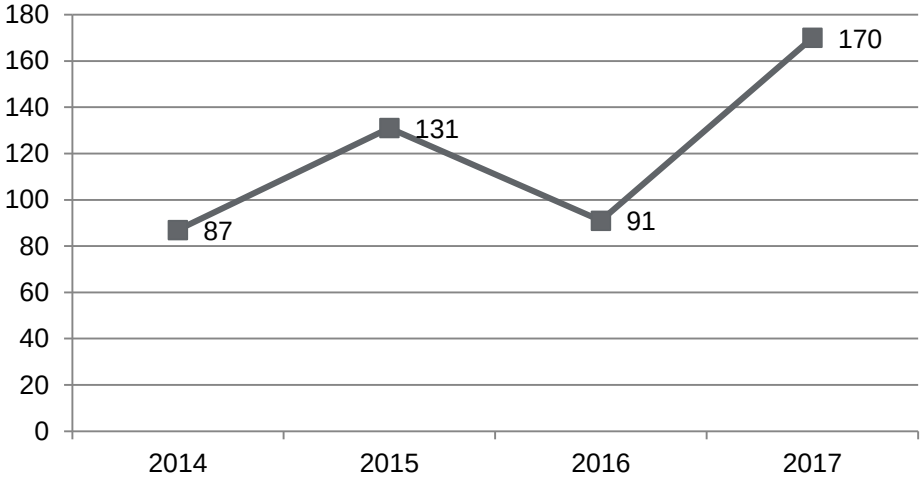
- Legal actions in case of fraudulent activities (Year 2015-2017 Summary)
  - Finished inspections on 313 NDA applications
  - 38 NDA may have the fake data, 30 NDA were rejected
  - Legal actions against to 11 sites and CROs

- 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

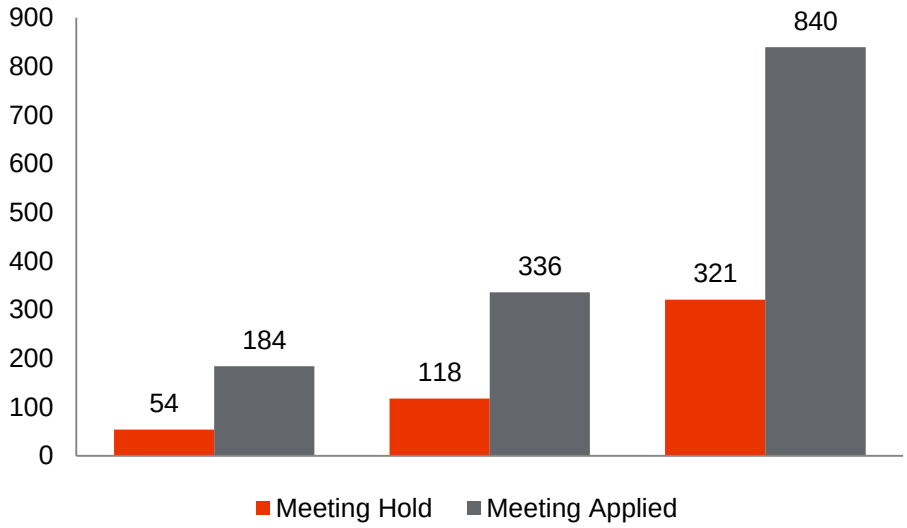
- Encourage China innovative drug to be developed in parallel with other global countries
- Number of chemical innovation IND approvals increased to 170 in 2017
- The average IND first-round review timeline was 120 working days
- The average priority IND first-round review timeline was 39 working days
- 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

NDA Acceleration

Global Data for China NDA

Global Data for China NDA

Gardasil 9

8 days, global data only

20Apr2018: NDA Applied
28Apr2018:
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
Jul2016: China approval

Urgent Unmet Need & Rare Diseases

Oncology Medicine NDA Approval closely after US-FDA

15Jun2018: Nivolumab
25Jul2018: Pembrolizumab

Rare Diseases

11May2018:
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_1yPgxr52MpLMRlZUA

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)

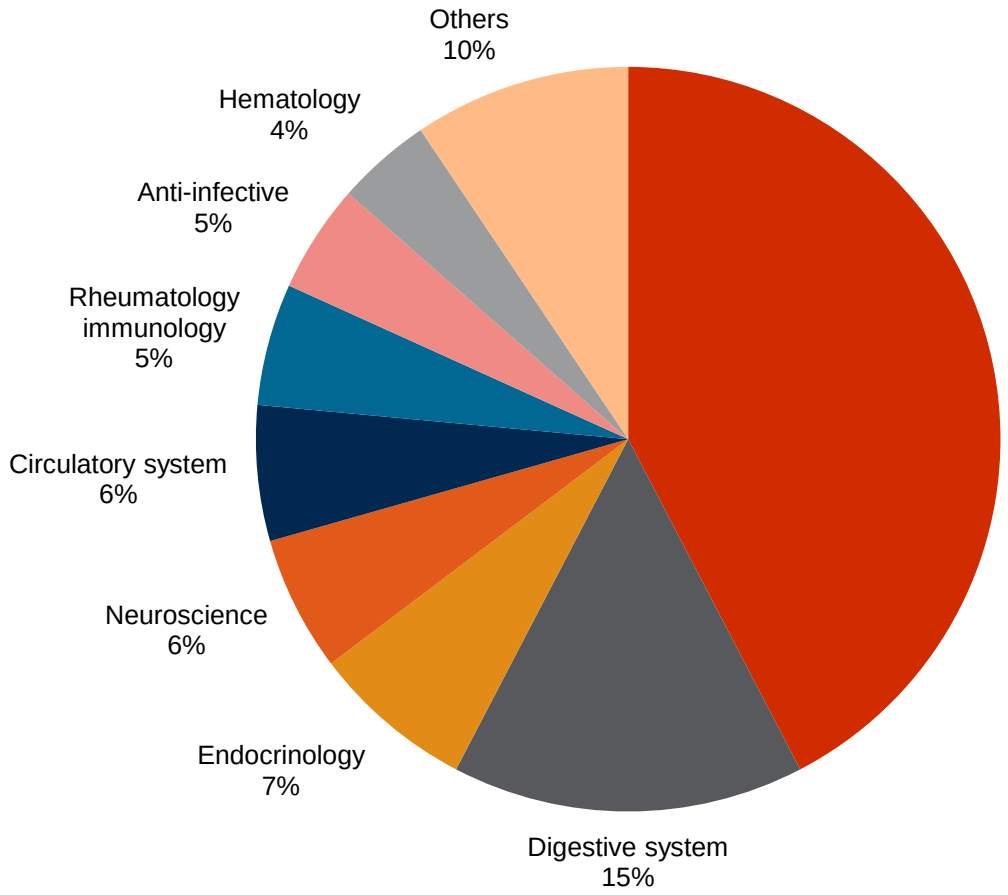
Decreasing Need

- 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.

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

Marketing Approval in China:

15Jun2018: Nivolumab (Opdivo, BMS) for lung cancer

25Jul2018: Pembrolizumab (Keytruda, MSD) for local advanced or metastatic melanoma.

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

	A	B	C	D	E
HCC	Y	Y			Y
NSCLC	Y	Y	Y	Y	
Esophagus Cancer	Y	Y	Y	Y	Y
Melanoma		Y	Y		
Hodgkin Lymphoma	Y	Y		Y	
T-Cell / NK-Cell Cancer	Y	Y		Y	
Urothelium Cancer	Y		Y		
Gastric Cancer		Y			Y
SCLC		Y			
Breast Cancer			Y		Y
Renal Cancer			Y		
Nasopharynx Cancer		Y	Y		

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


Early Phase


First in Class


China only registration

- 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