HOW CHINA REGULATORY REFORMS ARE CHANGING THE PHARMACEUTICAL INDUSTRY

The National Medical Products Administration (NMPA) is the Chinese agency for regulating drugs and medical devices (formerly the China Food and Drug Administration or CFDA).

DEVELOPMENT HISTORY

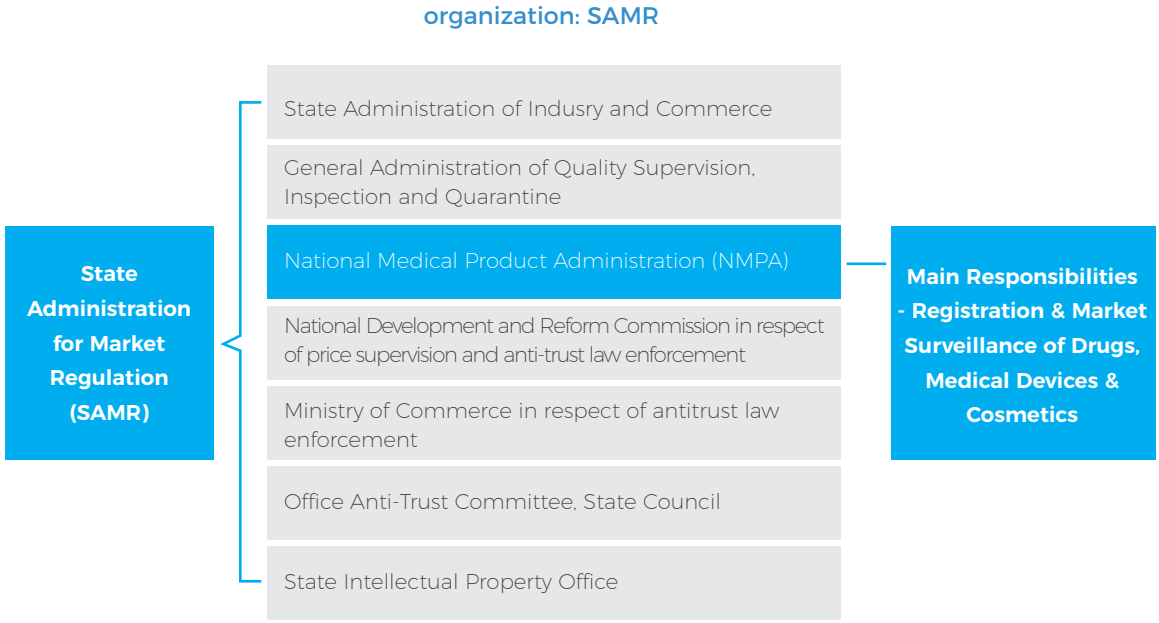
- Before 1998, the entire industry, including drug manufacturing, pricing, and distribution, was managed mainly by state-owned companies under loose guidance from provincial branches of the national Pharmaceutical Administration.
- 1998 State Drug Administration (SDA) was set up and regulator power began to centralize.
- 2003 SDA became the State Food and Drug Administration (SFDA)
- 2013 SFDA renamed to CFDA and became standalone agency
- March 2018, China restructured the China Food and Drug Administration (Known as CFDA) to National Medical Products Administration (Known as NMPA)
- 1st September 2018, the new name of NMPA was adapted

MAJOR DIFFERENCES

- NMPA focuses on pharmaceuticals and medical devices. CFDA focused on food and drugs.
- NMPA is elevated to a ministerial-level agency and ministered by the State Administration for Market Regulation (Known as SAMR)
- SAMR is not responsible for food administration and instead is designed to raise China's drug regulation to international standards.

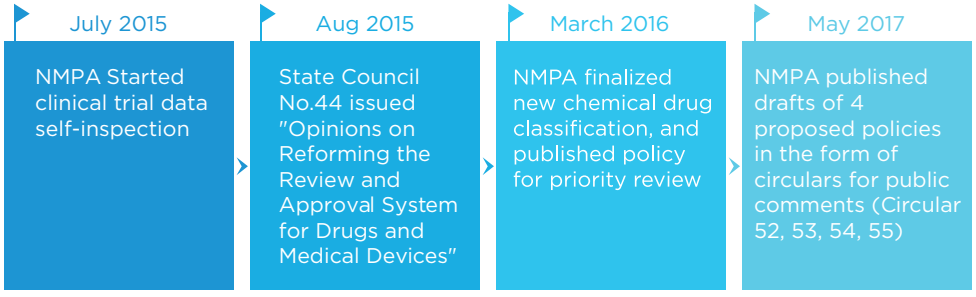
MAJOR ROLES OF NMPA

- Drafting laws and regulations for drugs, medical devices, and cosmetics
- Establishing medical device standards and classification systems



THE REFORM

Since 2015, the NMPA has initiated a series of reform documents, with the purpose of pushing the Chinese pharmaceutical and medical device industry to a more mature and globalized environment.



China is currently recognized as the world's second largest pharmaceutical market. However, the regulatory policies have been very challenging for many large foreign pharmaceutical enterprises, as well as innovative local companies. Some of the reasons for those challenges are:

- Complicated and long review processes compared to most major countries.
- Limited clinical trial quality checks with no enforcement mechanism, which has caused issues when compared to international standards.
- Lack of people in regulatory bodies which has caused a 20000+ backlog and long queue time for approval.

Subsequently, the Chinese pharmaceutical industry has fallen behind many other countries in terms of drug innovation as well as drug efficacy, safety, and quality.

With these new innovative reform policies, the NMPA will "promote the structural adjustment, transformation and upgrade of the pharmaceutical industry and bring marketed products up to international standards, so as to better meet the public needs for drugs." (NMPA, 2017) There are 3 major aims with these new policies:

- Achieve faster review times and eliminate the backlog of registration applications.
- Encourage innovative drugs to catch up with international development.
- Establish an environment to enhance drug quality and safety.

ACHIEVING A FASTER REVIEW

In the past, the review process of new drugs has been extremely slow due to repetition of generic drug applications, and lack of employees in CDE (Center of Drug Evaluation). In 2015 there were approximately 70 reviewers to handle an annual load of more than 7,000 drug applications. Compared with the United States, Chinese citizens in average need to wait 8 more years to use new drugs in the healthcare system.

This reform not only increased the number of reviewers from 70 to 600 by late 2017, but also optimized the drug registration process by:

- Creating a priority review channel opened for selective drug categories such as innovative and orphan drugs.
- Encouraging new drugs from global pharmaceutical companies to undergo clinical inves tigation within China and outside China in parallel; shortening drug delays (time period be tween approval outside China and approval inside China).
- Allowing the foreign drug registration process to be changed from "3-submission-3-approval" to "2-submission-2- approval" while eliminating the CPP requirement. (Wang, 2017)

NMPA has issued guidelines for priority review and approval...

Priority approval criteria

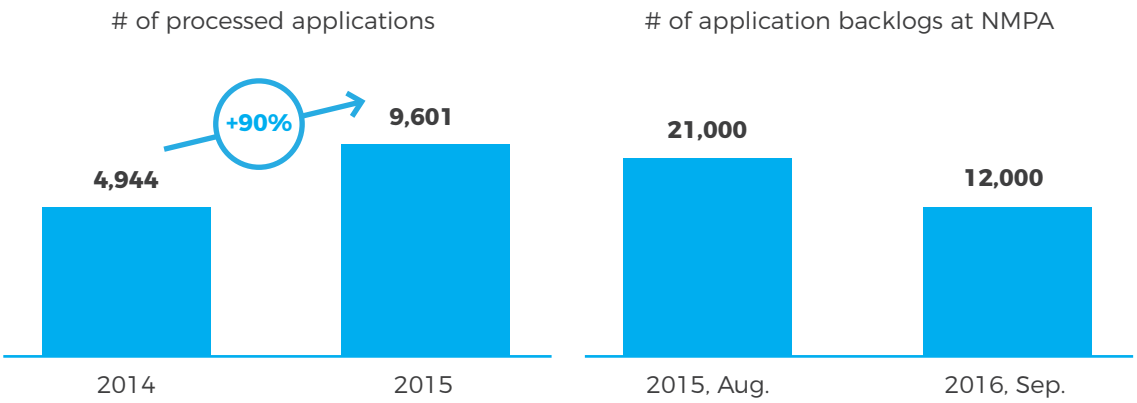
2015.07 NMPA published "Drug registration acceleration" (draft) **2015.11 NMPA** published "Opinions on product registration" (Order 230) **2016.02 NMPA** published the "Priority approval" policy (Order 19) **Now**	Demonstrating clear clinical value	· New-to-world innovative drug · Localized manufacturing of new-to-world innovative drug · Advanced formulation technology, innovative treatment approach, with clear dinical value
		· Gx application close to patent expiry (CTA application: 3 year prior to patent expiry; NDA application: 1 year prior to patent expiry)
		· Synchronized new drug CTA application in EU/US and approved in EU/US
		· Synchronized NDA application between China and US/EU, using China local manufacturing facility that passed cGMP
		· TCM with therapeutic advantage in critical disease
		· Innovative drug (National award winners)
	In priority TAs	· AIDS
		· Tuberculosis
		· Hepatitis
		· Rare disease
		· Tumor
		· Pediatric disease
		· Geriatric disease
	Other	· Gx applications: that withdraw the current applications and apply under the new regulations
		· IND/NDA for drugs urgently needed or severely short in the market
		· Supplementary applications for changed manufacturing process or technology in generics quality consistency evaluation

Criteria with prioritized drug lists published already

Source: NMPA

The results so far: After only a 16-month approval from the US FDA, AstraZeneca China announced on March 2017 that Tagrisso (osimertinib AZD9291) obtained marketing approval from the NMPA for non-small cell lung cancer (NSCLC) indication. This would have taken 3-5 years before the reform.

CDE has significantly accelerated review and approval process

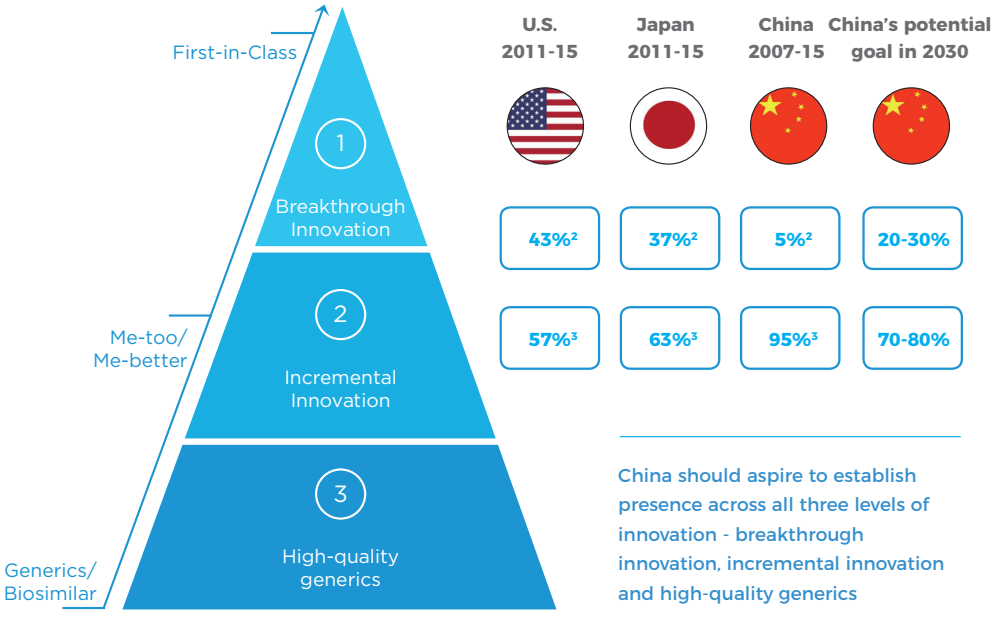


McKinsey & Company

ENCOURAGING INNOVATION

China has a large amount of domestic drug manufacturers, most of the 5000 companies are small to medium size and focus on making generic drugs, including many traditional Chinese medicines. Under huge from competition within the generic drug market, few manufacturers are actually motivated to invest in innovative new drugs. According to McKinsey & Company, 95% of drugs in China currently are generic drugs, while only 5% are New Molecular Entities (NMEs). For comparison, the innovative drugs percentage in Japan is 37%, and 43% in United States.

3 levels of innovation



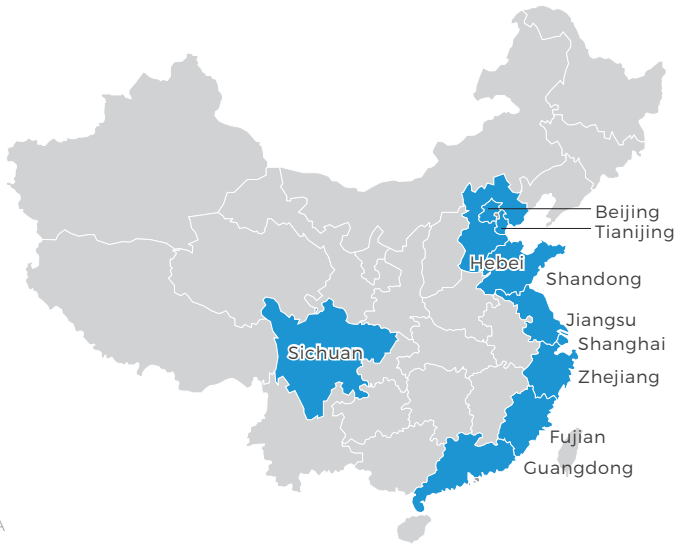
China should aspire to establish presence across all three levels of innovation - breakthrough innovation, incremental innovation and high-quality generics

Source: FDA

To change the current situation, the NMPA had to come up with many policies which favor pharmaceutical innovators by:

- Prioritizing the review and approval process for innovative drugs: As the CDE expands with more people, more innovative drugs will enjoy the "Green Channel" review process without a long delay due to the backlog.
- Allowing the MAH scheme to issue separate license holders and manufacturers:
    - Marketing Authorization Holder (MAH) allows research and development institutes or agencies to apply for drug approvals from outsourced manufacturers. This will encourage local biotechnology and pharmaceutical research institutes to conduct drug development without having manufacturing capabilities. It will also provide flexible options for multinational pharmaceutical giants, such as becoming a Certified Manufacturing Organization (CMO) for a MAH. Currently, MAH is piloted in 10 provinces for 3 years as outlined in the image below.

Pilot provinces



Source: NMPA

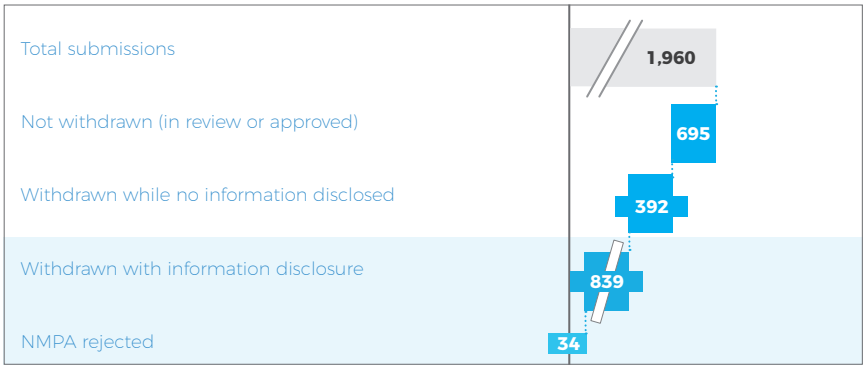
- Protecting innovators' rights: Among the 4 Circulars published in May 2017, Circular 55 proposed to set up an effective drug-patent linkage system. The patent holder will have 20 days to file an infringement claim and notify the CDE of the case. In that situation, the CDE will continue its review of the registration application but will not issue an approval for either 24 months or until the patent case is resolved, whichever is shorter. If the court rules that the patent is not infringed, then the NMPA will approve the drug once its review is complete. (Covington, 2017) This recent circular proposition further protects the innovators' rights and patents and will surely incentivize more companies into drug innovation.

ENHANCING DRUG QUALITY

The low quality of drugs made in China has become a widely accepted fact among Chinese citizens. People would prefer to spend 3 times or more on imported drugs, even if it shares the same formula with domestic drugs. To ensure Chinese drug makers can meet international standards, the NMPA proposed the following reform actions:

- **Self-Inspection:** Due to inaccurate and incomplete clinical data that happened in previous submissions, the NMPA launched a self-inspection program in July 2015 that aims to check the authenticity of clinical data across CROs, and clinical sites. The NMPA also mobilized their experts to check their data authenticity and the result was shocking. By Oct 2016, 65% of 1960 applications were withdrawn or rejected by NMPA due to low quality registration data.

Scope of self-inspection



Source: NMPA

- **Quality Consistency Evaluation (QCE):** Since the quality of approved generic drugs in China varies widely, the NMPA initiated the QCE in Mar 2016 that requested generic drug manufactures to conduct consistency and efficacy research and submit the evaluation by the end of 2018. The purpose is to further improve the quality of generic drugs and ensure their efficacy could meet the originators' standard.

- **Good Manufacturing Practice (GMP) and inspection:** The NMPA also launched a set of initiatives to further screen low-quality drug makers. With the increasing capacity of the NMPA, there will be more unannounced inspections of clinical sites. Manufacturing processes and quality control will be inspected by provincial-level FDA, while sales and marketing processes will be inspected by city-level FDA. (Wang, 2017)

MORE GLOBAL INVOLVEMENT

The International Council for Harmonization (ICH) is a global organization which works to standardize drug regulations around the world. As China recently joined ICH, in Aug 2017, the NMPA pledged to gradually transform its regulatory authorities, industry, and research institutions to implement international technical standards and guidelines. It also claims to actively promote the faster entry of international drugs into the Chinese market, as well as support the innovation and competitiveness of its domestic pharmaceutical industry. (FDA, 2017)

For multinational pharmaceutical companies, the NMPA's significant reforms are bringing more business opportunities to the Chinese market by:

- Creating a new classification on new drugs based on the globally aligned model, which makes it closer to other international regulatory agencies.
- Reducing the drug lag with a faster and simpler review and approval process.
- Accepting foreign clinical data means the NMPA marketing authorization approval will be in parallel with the United States and Europe.
- Encouraging foreign new drug investment to come to China and set up research centers.

For local Chinese pharmaceutical companies, the reform is bringing challenges as well as opportunities, such as:

- The Quality Consistency Evaluation (QCE) will remove many smaller, low-quality manufacturers, as the quality focused drug makers will have a bigger market share.
- Drug makers with strong R&D capabilities will benefit from the reform, as many of the new policies favor innovative drugs.

Increasing the quality and meeting international standards will make Chinese pharmaceutical companies more competitive in overseas markets. The NMPA reforms bring unprecedented changes to the Chinese pharmaceutical industry. Multinational pharmaceutical companies will need to familiarize themselves with these new changes and their implications. To begin working within the new framework and regulatory environment, it is essential to have China integrated in any clinical development and marketing plan. In China, the stricter policies will enhance local drug makers' quality and help them meet these global standards. From now on, China will not be the sole market for Chinese drug makers, but rather grow as an open market to the world.

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