REGULATORY FOCUS

China's Evolving Regulatory Environment: Special Report

By Alistair Davidson, Guoliang Liu and Bill Wang

This article provides an overview of the clinical trial Investigational New Drug (IND) approvals and New Drug Application (NDA) approvals in China for locally developed and foreign-developed new drugs, based on information from the database and annual report of China's regulatory authority, National Medical Products Administration (NMPA). The authors assess how the clinical trial market has responded over the past few years and analyzes the future of the China market. They also review the key consideration principle by NMPA for new drug investigation on urgent/unmet medical needs.

Introduction

China's drug and medical device regulatory environment has changed dramatically in the last four years, with various reforms initiated since August 2015 when China's central government issued its notification, "Opinions on Reforming the Review and Approval System for Drugs and Medical Devices." The notification aim to eliminate the backlog of drug applications, upgrade the quality of generic drugs, encourage new drug R&D in line with global development and improve the quality and transparency of the review and approval process.[1]

Following the notification's issue, the authors have observed several policy improvements over the last four years, including:

- The new drug review timeline has been shortened significantly. The clinical trial IND timeline, which had taken one to two years prior to 2015, has been reduced to about three months (60-working-day silent approval).
- The National Medical Product Administration (NMPA, previously CFDA or SFDA) joined ICH as a full regulatory member in July 2017. Some International Council for Harmonisation (ICH) guidelines have been implemented with others scheduled to be implemented soon.
- Some regulatory hurdles, such as the requirement for three-submission-three-approval, First-In-Human (FIH) Phase I trials in China and foreign Certificate of Pharmaceutical Product (CPP) needed for China NDA submission, were eliminated, making it possible for new drug development in China to run in parallel with timelines in the US and EU.

In response to these changes, contract research organizations are making significant strategic investments in China to expand their access to the country's evolving drug development and post-marketing ecosystem and enhance Chinese biotech companies' ability to conduct trials in the global market. Recent regulatory changes have helped simplify the drug development approval process in China. As a result, biopharmaceutical companies increasingly consider China a key country for conducting clinical trials across many, if not all, global studies and are seeking CRO partners who understand the regulatory landscape. The goal is to develop optimized regulatory and access strategies and to facilitate more efficient and robust generation of the evidence of value, safety and effectiveness needed to obtain approval and access in the Chinese market.

New Drug R&D has Grown Significantly

In China, the Center of Drug Evaluation (CDE) is the key drug reviewing entity under the NMPA. The CDE issued its 2018 annual report on 1 July 2019, demonstrating how the clinical trials and new drug development market has grown in China with many new drug clinical trials have been approved in China.[2] **Figure 1** shows the number of new chemical drug IND approvals nearly doubled from 2014 (87) to 2018 (172).

In addition, the new drug classification was changed in 2016. Previously, a "new drug" meant new chemical or biological entities not approved in China; now "new drug" means entities not approved anywhere else in the world. This explains why the 2014 and 2015 data are as high as they are as they include approvals for the "new drugs" or those already approved in foreign countries, but not in China.

New biological product IND approvals increased even more substantially from 2014 to 2018. **Figure 2** shows the number of new biological product clinical trials approved more than tripled (from 110 to 349) during that time.

Figure 1. New Chemical Drug IND Approvals, Counted by Compounds

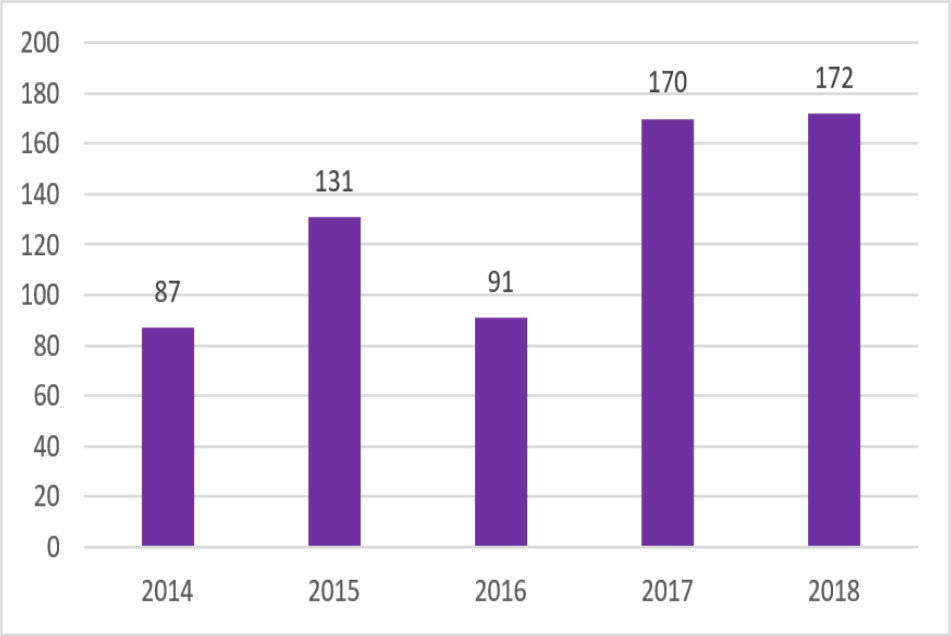


Figure 2. New Biological Product IND Approvals From, Counted by Number of Applications

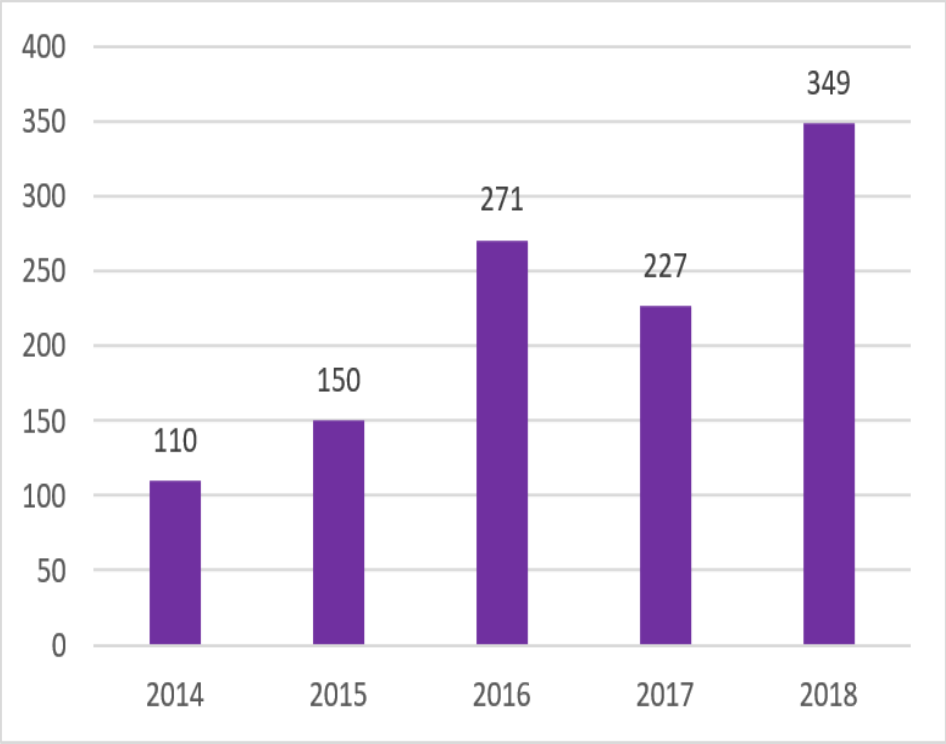
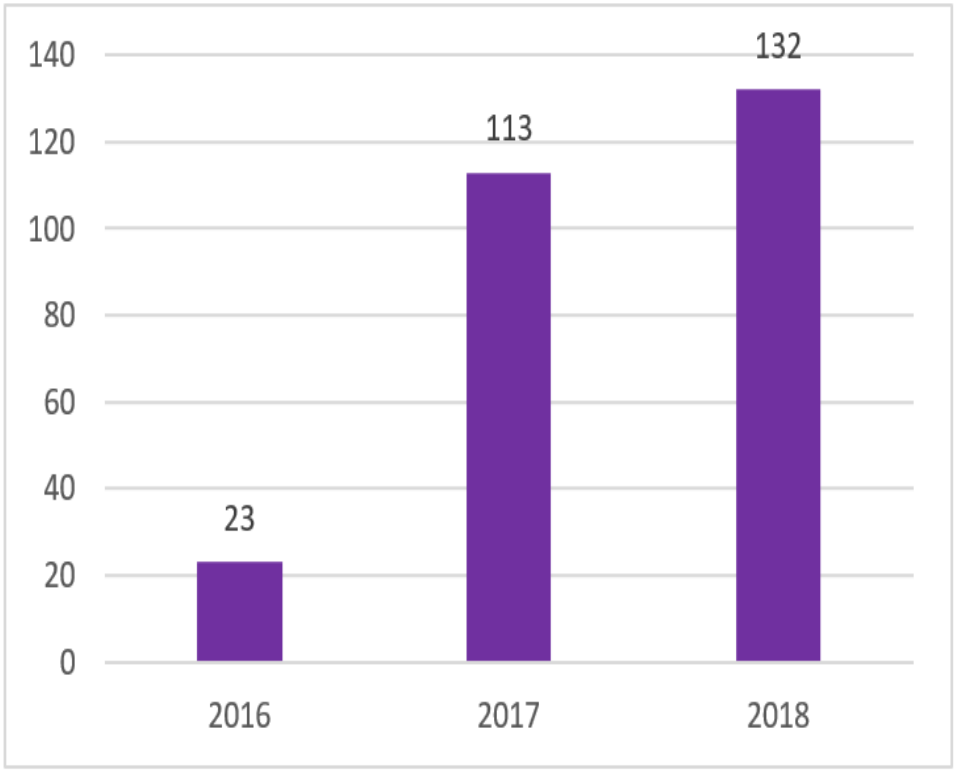


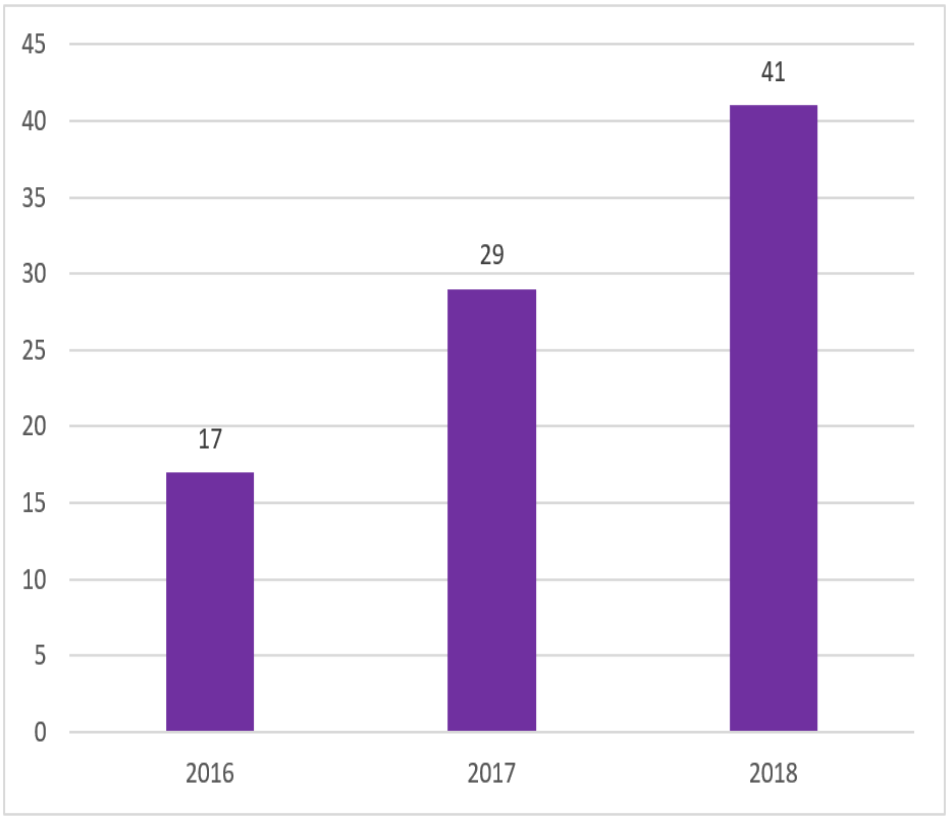
Figure 3 shows the fast pace at which the number of new chemical drugs approved in China has grown from 2016 (23) to 2018 (132).

Figure 3. New Chemical Drug NDA Approvals, Counted by Number of Applications



Meanwhile, **Figure 4** shows the number of new biological products approved in China also grew very quickly from 2016 (17) to 2018 (41).

Figure 4. New Biological Product NDA Approvals, Counted by Number of Applications



Assessing the Trends

In reviewing the CDE annual report and the information on clinical trial approvals and new drug registrations noted previously, a number of changes emerged. For example, with the hiring of new drug technical reviewers by the CDE, the reviewer team has grown and strengthened. As a result, the application backlog has reduced significantly, from a high of 22,000 in September 2015 to less than 3,500 by the end of 2018.

Because of the influx of staff, the CDE now has sufficient resources to keep close communication with applicants via a variety of pre-submission consultation meetings and ensure reviewers are dedicated for priority review and complete project review within the promised dates. To strengthen the quality of clinical trials performed in China, in July 2015 CFDA began requiring all trial sponsors to conduct trial data self-inspections, which would then be audited by CFDA. This requirement had a significant impact on the local China pharmaceutical industry as it requires companies to ensure their data and trials meet global standards in an environment where, up until this time, such standards were sometimes ignored. As a result, the number of total drug applications declined dramatically in 2016. At the same time, CFDA encouraged local and foreign new drug innovations by offering a variety of incentives, such as priority review treatment, shortening the review timeline and process, new Marketing Authorization Holder (MAH) policy and joining ICH. These initiatives caused drug

applications to grow quickly in 2017 and 2018 **(Figure 5**), with many global trials initiated by foreign sponsors and emerging local new drug and new biotechnology innovators.

Figure 5. Acceptance of Various Applications From 2015 to 2018

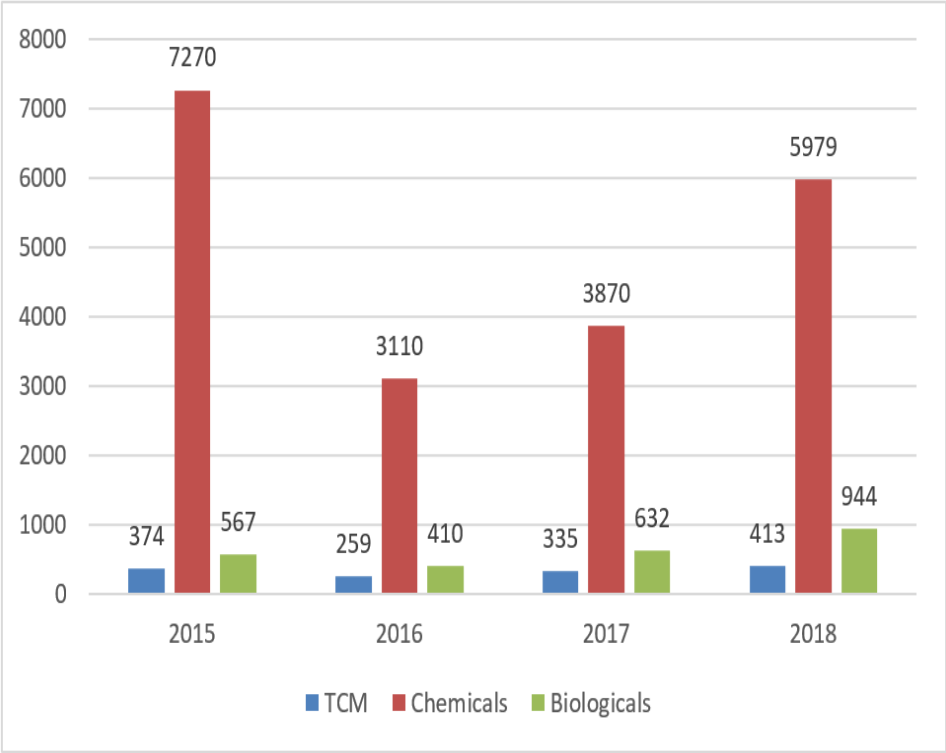


Figure 5 note: Traditional Chinese Medicines (TCM)

Priority review and pre-submission consultation meetings are important practices for encouraging new drug innovation and have been well-established by leading regulatory authorities in the US, EU, Japan and elsewhere for many years. However, due to resource shortages before 2016, even though a similar practice did exist, CDE routinely rejected requests or was not able to meet expectations. Since then, there have been major improvement due to the increase in reviewer resources.

In 2018, 313 applications were granted priority review. The CDE has specific criteria on how to grant priority review to the projects. These include such factors as a new drug developed in parallel with the US or EU, whether the drug has significant clinical value, whether the drug is indicated for pediatric use and rare diseases. Among the 106 new drugs approved in 2018, 83 of these have benefited from this process with much shorter IND and NDA review timelines.

CDE also has become more open to drug applicants. Formal consultation meetings are important for drug sponsors to communicate directly to the drug reviewers. In 2018, there were 1,982 meeting requests from different applicants, including 824 (42%) for pre-IND and 555 (28%) for pre-NDA. Applicants have other options to make requests during the IND evaluation, post-

Phase I or post-Phase II. Among the 1,982 meeting requests, 322 (16%) resulted in final face-to-face meetings, a significant increase in meeting requests compared to 2017 when there were 840 meeting requests and 321 (38%) final meetings. Based on experience with pre-IND requests, CDE reviewers will clearly answer the questions from applicants, although it is not necessary to hold face-to-face meetings.

Thanks to a more favorable clinical trials and drug registration environment, coupled with much shorter IND and NDA review timelines, there were 106 new drugs approved in 2018, including six locally developed Class I (i.e., first in world) new chemical entities and three new biologicals (the most in China's history), as well as 67 innovator drugs from foreign countries.

China's local new drug innovators are now playing a significantly more important role in the market. As Figure 6 notes, domestic NCE applications have increased 74% from 2014 (66) to 2018 (115). Meanwhile, as **Figure 7** demonstrates, the number of clinical trial approvals by domestic applicants in 2018 (297) was 480% higher than in 2014 (51).

Figure 6. Chemical Drug NCE Applications Accepted by CDE, Counted by Compounds

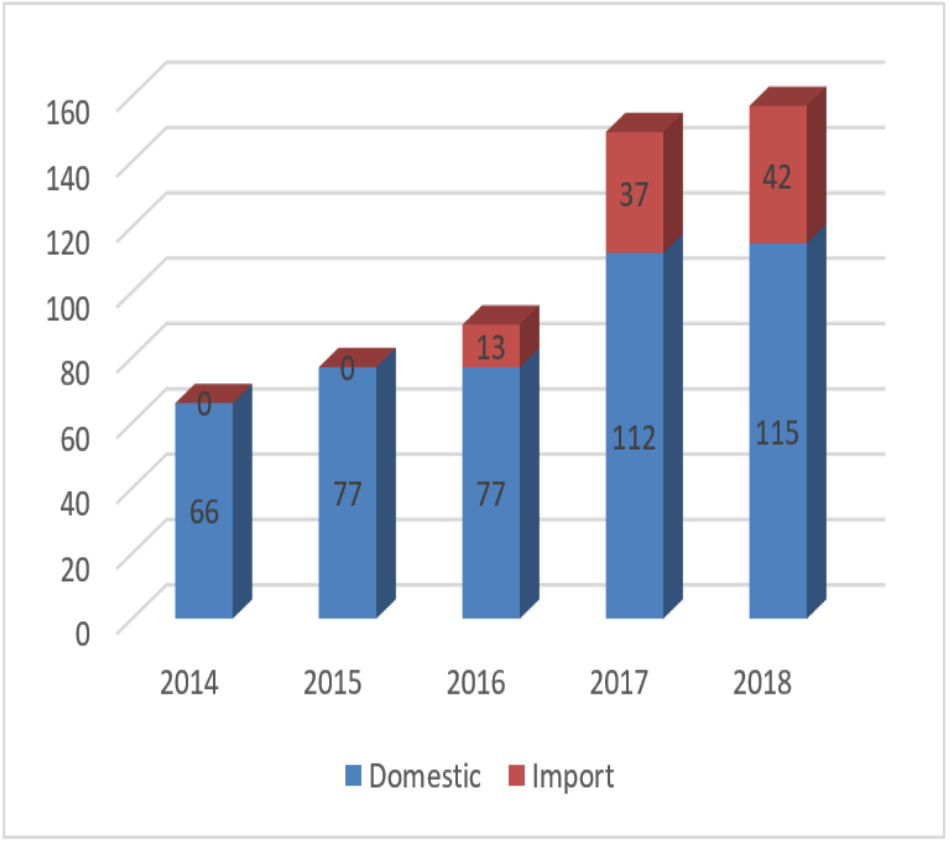
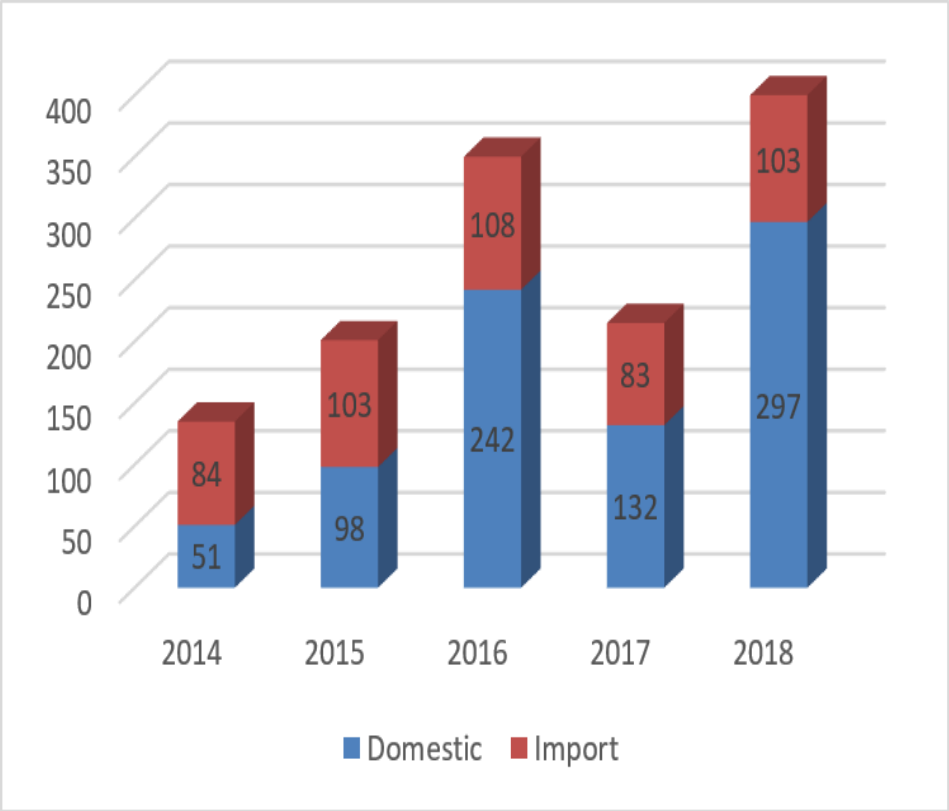


Figure 7. New Drug Clinical Trial Approvals by CDE, Including Chemical and Biologicals, Counted by Compounds



Local China Players: Some Observations

As noted in Figures 6 and 7, local new drug innovation in the China market has caught up with and surpassed global players. Due to regulatory reform and policy changes, many new drug and biotech innovators are significantly stepping up activities, venture capital is being injected, and talented Chinese R&D professionals are coming back to China, all of which is contributing to a boom in China.

Many local companies have moved from the manufacture and supply of quality generic products into innovative R&D, including full-blown clinical development in China and elsewhere. These companies have a range of new drugs in development and, in the next five to 10 years, these will start to be approved and launched in China and the rest of the world. Investment in these companies is significant and increasing as their future potential grows.

There are also a host of recent examples of licensing deals between new Chinese innovators and overseas companies as the stability and potential of these companies can afford an efficient and effective route to development, approval and commercialization of their partners' drugs in China.

Projecting the new Drug Development Market in China

Today, China has caught up with and surpassed Japan to become the second largest pharmaceutical market in the world. More importantly, China is growing faster than both the US and Japan, making it attractive for local and global pharmaceutical and biotech companies.

Furthermore, the Chinese government's main purpose with this regulatory reform is to encourage local and global new drug innovation to meet the needs of Chinese patients, while discouraging the development of high-competitive, low-quality generic drugs.

This initiative has led to the boom of new local China drugs, especially new biotech research. These include:

- In China, there are some CAR-T projects reaching the point of application for clinical trials.
- Some foreign and local PD-1/PD-L1 projects at clinical trial stage, NDA and even marketing authorization.
- The first biosimilar product approval in China in February 2019, and many biosimilar products are at clinical trial and NDA stage.[3]

Expectations are that after the US, EU and Japan, China will become the next "hot" area for new drug development. Expect also there will be more foreign sponsors undertaking global trials in China. Meanwhile, local China pharmaceutical and biotech companies will go outside their country for clinical development in the US, Europe and Australia. Foreign-developed new drugs will be approved in China in a much shorter time, while locally developed new drugs could be developed and approved in China and the US in parallel.

All the previous developments are contributing to the evolution across a wide group of stakeholders in China and present opportunities such as:

- New drug and biotech innovation and the development of new drugs and new biological products for China and the global market
- Contract research industry, such as CRO, CMO and central labs, etc.
- Clinical trial sites are currently all government-owned big hospitals mostly in large cities, all of which are GCP accredited by NMPA. Based on the new policy, GCP accreditation will no longer exist and the government is encouraging social investment in clinical trial sites. Currently, there are no private clinical trial sites. To build them will take time due to specific hardware and software requirements and the need for experienced investigators. It will be interesting so see the growth of new non-governmental-owned sites soon, especially Phase I units.
- Apart from innovation, there are additional opportunities for reformulating old drugs or developing new dosage forms (e.g., inhaler or transdermal drug delivery systems) and first-to-market generic companies.

Even under this open, harmonized environment and growing market, not all new drug innovations are welcomed or encouraged by NMPA and CDE. On the other hand, not all generic drugs are discouraged. There is strong encouragement for projects under priority review and special treatment with much shortened review timelines, while discouraged products may take much longer time and may be challenged or rejected by authorities. As the following section further describes, key criteria will be therapies for treating urgent and/or unmet medical needs.

NMPA and CDE's Main Consideration: Urgent and Unmet Medical Needs

NMPA and CDE's main consideration for new drug approvals is to meet unmet medical needs. On 20 December 2017, NMPA issued "The Guideline on Conditional Approvals for Urgently Needed Drugs."[4] This guideline is clear on defining on unmet medical needs.

Unmet medical needs usually include:

- conditions without any approved therapy
- conditions where there is available therapy, but new drugs have an advantage over current therapies for the following reasons:
- obvious improvement on the disease's serious consequences
- significant efficacy compared to current therapy
- can be effectively combined with other key drugs, while current therapy cannot be the same efficacy as current therapy, but with a better safety profile (lower toxicity) or better or more compliance for patients
- resolves newly emerging or expected public health needs

Experience working with NMPA and CDE has shown a new drug's value can be assessed using the following criteria:

- Is there an available therapy? Is there any advantage over current therapies?
- Is it indicated for a life-threatening disease, a rare disease or pediatrics?
- Is it for the treatment of an infectious disease, such as HIV or HBV?
- Is it for the prevention of an infectious disease, such as a vaccine for public health?
- Is it less expensive, even if it has the same safety and efficacy as current therapies?

To address these issues and questions, several procedures have been implemented.

Procedures for the Evaluation and Approval of Foreign-Approved new Drugs With Urgent Medical Needs

On 23 October 2018, NMPA and the National Health Commission (NHC) issued this procedure with the central consideration that, due to long review timelines and drug lag, there are some innovative new drugs that have already been

marketed in the US, EU or Japan for many years.[5] However, they are not yet approved in China. Subsequently, CDE is responsible for arranging local experts to select some potential drugs approved in the US, EU or Japan, but not yet approved in China. These include drugs that are:

- indicated for a rare disease
- indicated for a serious life-threatening disease for effective therapy or prevention
- indicated for a serious life-threatening disease and has an obvious clinical advantage

For selected drugs, NMPA encourages drug holders to discuss drug registration as they will have specific channels for these applications. Applicants will have pre-submission consultation meetings with CDE reviewers showing the assessment on ethnic sensitivity or, if the drug is already marketed in Japan, Hong Kong, Taiwan or Macao, provide an evaluation report on the clinical and postmarket usage in these areas. Applicants have significant opportunities to submit an NDA directly to NMPA without any local trial requirement. Based on this specific regulatory pathway, NDA evaluation should be completed within three months for orphan drugs, or six months, as compared to one to two years for the normal prior process. Administration approval by NMPA should be completed within 10 working days, as compared to two months for the former process.

Based on the previous procedure, in November 2018 and May 2019, CDE released two lists of urgently needed new drugs.[6,7] A total of 74 new drugs were listed. All of them are already marketed in the US, EU or Japan, but not in China. Additionally, most of them are for rare diseases, such as Eliglustat, Velaglucerase Alfa and Taliglucerase Alfa (indicated for Gaucher disease) and Fingolimod, Dalfampridine and Lemtrada (Alemtuzumab) (indicated for multiple sclerosis). Apart from orphan drugs, some drugs that have a clear advantage over current therapies, such as Maviret (Glecaprevir/Pibrentasvir) for HCV because it is for public health, a serious life-threatening illness and has clear advantages.

CDE announced in its 2018 annual report that 10 of the listed drugs have been approved.

Conditional Approvals for Urgently Needed Drugs

On 20 December 2017, NMPA issued "The Guideline on Conditional Approvals for Urgently Needed Drugs."[8] This guideline is for the new drugs (TCM, chemical drugs and biological products not approved in China) with indications for serious life-threatening diseases and those without available therapy. The purpose is to shorten clinical trial timelines and provide earlier use for patients. Conditional approval could be granted based on:

- clinical trial results using surrogate endpoints or middle endpoints, which can predict efficacy and benefit

- early or mid-term clinical trial result, which can predict benefit and advantage over current therapy
- orphan drugs already approved in foreign countries

Acceptance of Clinical Trial Data Performed in Foreign Countries

On 6 July 2018, NMPA issued "The Guideline of Accepting Clinical Trial Data Performed in Foreign Countries."[9]

The principle of acceptance of foreign clinical data is summarized in **Table 1.**

Table 1. Foreign Clinical Data Acceptance Criteria

Acceptance of Foreign Data	If data compliant with ICH GCP	If data could support proposed indication, safety and efficacy	If the date indicates any ethnic differences	Follow-up action by applicant
Fully Accepted	Yes	Yes	No	Can support NDA in China, no local trial needed
Partly Accepted	Yes	Yes	Yes	Discuss with CDE, to evaluate if any local bridging study needed
Not Accepted	No	No	N/A	Need a full development program in China

Although this guideline is suitable for all drugs, NMPA and CDE have their own criteria as they view generic drugs as a lower priority although an applicant may have BE study data from foreign countries. Priority is given to new drugs with the potential to address unmet medical needs. The guideline clearly states "as for drugs indicated for serious life-threatening disease, or rare disease or for pediatrics, and without any currently available therapy, if the foreign clinical data is treated as 'partially accepted' after assessment, application can be treated as conditional acceptance of foreign clinical data, and result in a request for post-marketing collection of safety and efficacy data for further assessment."

Generic Drugs

Encouraging innovation does not mean discouraging all generics, as some may have benefits for lowering the price of innovator drugs. However, if there is only one player in the market, the result could be higher cost. If a drug is too expensive to be accepted by patients or accepted by social medical insurance, this represents another kind of unmet medical need and another reason why NMPA encourages first-launched generic drugs so long as the patent has expired and no other intellectual property issues exist.

In January and December 2018, CDE issued two lists of drugs to the local pharma industry, one listing drugs with their patents expired, terminated or

invalid and another citing drugs without any local generic in the China market.[10,11]

In total, 16 drugs are listed with clear statement that all 16 have specific medical value and are without patent protection. Clearly, CDE's intent is to encourage local pharmaceutical firms to produce these drugs, all of which still have potential market value and, thus, increase access to these drugs for the public.

Meanwhile, CDE offers priority review treatment on these patent-expired (or first-launched) generic drug applications. Based on CDE's 2018 annual report, among the 313 priority-reviewed applications, 25 (8%) fall in this category. Among 83 drug approvals via priority review process, 10 (12%) are patent-expired or first-launched generic drugs. This is compared to 2017 when among 50 drug approvals via priority review process 10 (20%) were patent-expired or first-launched generic drugs.

Finally, the most important development for the China pharmaceutical industry in 2019 was the August announcement regarding the passage of the new version of Drug Administration Law (DAL) previously approved and issued by the National Congress Committees.[12] This took effect 1 December 2019.

The current effective law dates to 1985. There have been many significant changes in this new version, which can be considered the over-arching law for the China pharmaceutical government and industry and the basis for policy and regulation by NMPA. It is clearly oriented toward unmet medical needs, as noted particularly by the following three clauses:

- Clause 16: encourages clinical-value-oriented new drug innovation, supports new therapeutic mechanism, multitarget research or new drugs with clear or specific efficacy, and encourages (including priority review) new drugs specific to pediatrics.
- Clause 26: for drugs indicating serious life-threatening disease without effective therapy or for urgent needs for public health issues. If its mid-term clinical trial result can show benefit and efficacy and predictable clinical values, conditional approval can be granted.
- Clause 96: encourages research and manufacture of drugs in short supply. Will have priority review on urgent short-supplied drugs, and new drugs for preventing serious infectious diseases or rare diseases.

Apart from encouraging new drug innovation to meet unmet medical needs, there are other new policies or systems that were not covered in the previous version. These include:

- Drug Marketing Authorization Holder (MAH) system, which refers to enterprises or R&D institutions that hold a drug approval license. The legal representative and the principal responsible person of the MAH shall take full responsibility for the quality of the drug products.

- The drug traceability system, in which NMPA should formulate unified drug traceability standards and regulations, drive mutual communication and sharing of drug traceability information.
- The pharmacovigilance (PV) system, in which NMPA should establish a system to monitor, identify, evaluate and control adverse reactions or other responses related to drug usage.

These new policies and systems are important for strengthening drug administration, ensuring drug quality, protecting the public's medication safety and legitimate rights and interests, all while protecting and promoting public health.

One common question for global regulatory agencies is how to use Real-World Evidence (RWE) to complement randomized clinical trials in evaluating the efficacy and safety of drugs. China is also considering how to respond to this question. For example, CDE issued its "Key Considerations in Using Real-World Evidence to Support Drug Development" in May 2019 to "provide clarity on the definition of real-world research, outline the use and scope of real-world evidence in drug R&D, explore the basic principles for the evaluation of real-world evidence, and consequently provide scientific and practical guidance for the industry to consider when utilizing real-world evidence to support drug development."[13] The draft defines RWE and provides scenarios where RWE supports drug development and regulatory decisions.

DAL also incorporated some recent improvements and achievements into regulations, such as a new management system for clinical trials, priority review and conditional approval, management of drug standards, postmarketing management system and a strong sanctions system. These new regulatory topics are also important in consolidating the results of the regulatory reforms instituted since August 2015.

Conclusion

Since China's regulatory reform started in 2015 there have been many policy introductions and improvements. These have markedly stimulated enthusiasm for new drug innovation and venture capital, with many enterprises committing to new drug and biological product research in China. This reform also has attracted foreign pharmaceutical and biotech companies to conduct clinical trials and have their drugs registered in China. From CDE's 2018 drug review annual report, this growing trend is clear and is having a significant impact on China and the global pharmaceutical, clinical trial and CRO industries. Many companies not previously considering including China in their clinical development ventures or as a market for new drugs are now actively pursuing such activities. This is a trend expected to continue.

The importance of addressing unmet or urgent medical needs cannot be underestimated for drug researchers and manufacturers. This does not mean all new drugs are welcomed, nor are all generics discouraged by NMPA. However, any pharmaceutical company or innovator, before commencing R&D activities in

China, must conduct a careful market to ascertain the urgent or unmet pharmaceutical needs in China.

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Cite as: Davidson A, Liu G and Wang B. “China’s Evolving Regulatory Environment: Special Report.” *Regulatory Focus.* January 2020. Regulatory Affairs Professionals Society.