

An overview of major reforms in China's regulatory environment

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Abstract

A series of regulatory changes and improvements in China commenced in July 2015. This article analyses the implementation of these reforms and their potential impact on clinical development in China, as well as the local and global pharmaceutical industry in the short and long term.

Introduction

It is widely recognised that China is currently the second largest pharmaceutical market in the world. Historically the regulatory environment in China has been considered a highly challenging one, with: (1) major issues in the areas of comparative quality between international standards and some local products and manufacturers; (2) a timeframe for review and approval of new drugs that is longer than most major countries; and (3) a lack of capacity in the regulatory bodies that has resulted in a backlog of applications.

In August 2015, the China State Council issued “Opinions on Reforming the Review and Approval System for Drugs and Medical Devices.” This was partly a result of dialogue with the local and international pharma industry that, for many years, has been pressing for major regulatory reform.¹ The overarching intention of this was to “promote the structural adjustment, transformation and upgrade of the pharmaceutical industry and bring marketed products up to international standards in terms of efficacy, safety and quality, so as to better meet the public needs for drugs.” The main practical aims are to: (1) eliminate the existing backlog of registration applications; (2) establish an environment for maximising the quality of generic drugs; (3) create a framework in China that encourages research and development of new drugs in line with global development; and (4) improve the quality and increase transparency of the review and approval process.

The pharmaceutical industry in China

China has a large domestic drug industry, comprising around 5,000 manufacturers, most of which are small or medium-sized and with a business based on generics, active pharmaceutical ingredients (APIs) or traditional Chinese medicine (TCM). Many generic drugs have dozens of approved manufacturers and there is little official

guidance for – or planned evolution of – the generics industry. The China Food and Drug Administration (CFDA) recently published “restricted” and “promoted” categories of generic drugs, which signals a move toward more logical control, direction and guidance of the generics industry.

Because of high competition in the generics area, local companies have not been motivated to invest in innovative new drugs, so their current capacity for such development is low. However, these companies do have manufacturing facilities that meet global good manufacturing practice (GMP) standards. Traditionally these generics companies have primarily relied on bioequivalence (BE) trials for generic drug registration. However, these companies now face the challenge of CFDA's new requirements on generic drug quality and efficacy consistency evaluation. For example, data considered inaccurate or incomplete will not be accepted and potentially existing licences could be revoked.

Regulations previously have strongly linked manufacturing with the licence holder, ie, the marketing authorisation holder (MAH) should also be the owner of the drug manufacturing plant. The announcement of the separation of these activities will create a more flexible, modern framework in which research companies can be the MAH and have the ability to contract manufacture to another party.

Impact of reforms

There are several areas where reforms will have a positive impact. Five of these are summarised here:

- **Self-inspection of clinical data.** Due to past instances of the submission of inauthentic or incomplete clinical data, CFDA launched a self-inspection programme for clinical data requiring applicants, contract research organisations (CROs) and clinical sites to self-inspect 1,622 registration applications pending approval. This initiative began in July 2015 and uncovered inauthentic and incomplete data with accompanying disapproval or investigations for appropriate cases by CFDA. CFDA also mobilised its experts to inspect selected studies that were suspicious in terms of data authenticity. Additionally, for future new drug applications (NDAs), CFDA requires applicants to include a clinical trial self-inspection report, which CFDA will further review.^{2,3} After 12 months (as of July 2016), CFDA reported that around 90 percent of the 1,622 applications have been withdrawn by applicants or rejected by CFDA.⁴
- **Priority review.** CFDA needed to put in place a system to encourage local and international new drug innovation to meet unmet medical needs and to encourage overseas sponsors to plan and perform clinical development in China in parallel with the US, EU and other countries. In February 2016, CFDA announced a new priority review process to meet this need. Priority review status can be requested based on the following criteria:
 - Innovative drugs not approved anywhere worldwide

Table 1: Updated classification/definition of new drugs in China.

| New class | Definition | Local clinical trial requirement | Application process | Monitoring period |
|-----------|---|-------------------------------------|----------------------|-------------------|
| 1 | New drug not marketed anywhere globally | Phase I, II and III | New drug process | 5 years |
| 2 | Modified/improved new drug not marketed anywhere globally (eg, new formulation, new combination, new indication, etc) | Phase I, II and III | | 3–4 years |
| 3 | China-manufactured generic drug that is only approved outside China | Pharmacokinetics (PK) and Phase III | Generic drug process | N/A |
| 4 | China-manufactured generic drug that already is approved in China | Bioequivalence (BE) study | | N/A |
| 5.1 | Imported innovative drug, approved outside of China | PK and Phase III | Import drug process | N/A |
| 5.2 | Imported generic drug, approved outside of China | BE study | | N/A |

- Innovative drugs where there is a plan to transfer the manufacturing site to China
- Global clinical trial application (CTA) to China in parallel with the US or EU
- Innovative drugs for HIV/AIDS, viral hepatitis, rare disease(s), malignant tumours and paediatric indications
- Newly launched generic drugs.

After CFDA approves the priority review process request, applicants are given priority reviewer resources allocated by the Center for Drug Evaluation (CDE) and additional channels to communicate with and obtain quick feedback from the CDE/CFDA. Target approval time from submission is within six months. To date, this has worked effectively for applications submitted after February 2016.⁵

- **Additional CDE capacity.** Urgent action was needed to meet the CDE's target to reduce the backlog in drug review procedures to zero by 2018. In 2015 there were only around 70 reviewers to handle an annual load of more than 7,000 drug applications in the CDE. Following a new hiring exercise, 600 drug reviewers had been put in place by the end of 2016 with more hiring planned for 2017–2018.
- **Rationalisation of MAH system and new classification/definition of new drugs:**
 - **MAH.** The MAH system ensures that drug research and development institutions can obtain and hold marketing authorisation while taking responsibility for drug quality. This allows and encourages drug research and development institutions to transfer manufacturing to an established drug manufacturer with an associated site inspection in order to validate the manufacturing process. However, there is no need for a repeat of the drug technical review. This is a major incentive for local new drug innovators in China who can now hold marketing authorisation independently. This reform will be implemented in a phased manner starting with a trial in ten selected provinces, mostly on China's east coast, within three years. With this change, CFDA guides and encourages drug researchers/institutions to focus on R&D and alleviates the need to invest in their own manufacturing plants. Overall this aligns China to most of the rest of the world and should channel more investment into R&D.^{6,7}
 - **New classification/definition of new drugs – a globally aligned model.** CFDA has created a new classification, “new to the world”,

to replace the previous “new to China” category. This is based on the global marketing authorisation approval status and the location of the manufacturing site(s) (inside or outside China). This removes the previous definitions that were based on the specific status in China, and aligns classification more closely to other regulatory agencies (see Table 1).⁸

- **Generic drug quality and efficacy consistency.** The quality of generic drugs approved in China varies widely. To improve quality, the CFDA has required generic drug manufacturers to start drug consistency research on quality and efficacy with a target completion date by the end of 2018. A product list has been developed by CFDA to inform which generic drugs need this consistency evaluation.

For evaluation purposes, the comparator product should be the “innovator drug,” or a globally recognised similar drug. Innovator drug means the first marketed drug globally with the full data package to support its safety and efficacy. This would be the situation in which a generic company has previously performed the consistency evaluation, but the comparator was not the innovator drug, so the generic company must re-evaluate against the innovator drug.

Comparison studies include formulation, quality standard, crystal form, particulate size, impurities and dissolution profile and *in vivo* BE studies. Many generic drug manufacturers are seeking clarity on the requirements, and, as a result, CFDA commenced relevant training in August 2016 and is open to further applicants participating in future training.^{9,10}

2017 updates – Reforms start to take shape

On 17 March 2017, CFDA announced its decision to change the requirement on import drug registration.¹¹ Public consultation was invited with a deadline for responses of 20 April 2017. The main aims of the change are to encourage foreign-developed new drugs to undergo clinical investigation within China and outside China in parallel; shorten the drug lag (time period between approval outside China and approval inside China); and meet the medical needs for new drugs for Chinese patients. Key changes include:

- **Opening of first-in-human (FIH) Phase I trials to global development.** This removes the previous requirement, which means that for new chemical drug and new therapeutic biological products foreign applicants can have a *full* clinical development plan inside China, starting from FIH to proof-of-concept (PoC) trials

in parallel with the global development programme. This change effectively opens an FIH Phase I market in China. It is important to note that preventative vaccines still may not undergo a global trial inside China.

- **Simplified process.** The process changes from “3-submission-3-approval” to “2-submission-2-approval”. Previously, foreign-developed new drugs needed three submissions: (1) multinational clinical trial (MNCT) submission to request global Phase II or III trial in China; (2) after the drug has been approved and the certificate of pharmaceutical product (CPP) is available from the US or EU (or any other countries), submission to CFDA to request clinical trial waiver (requesting exemption from need to do any additional local trial); and (3) NDA submission to CFDA for market approval. Under the new policy, there is no need for the second submission (submission to CFDA to request clinical trial waiver) and the sponsor can move directly to the NDA/MAA submission. This simplified process will shorten the whole approval process by at least one year.
- **No need for a CPP for NDA/MAA submission.** Previously, CFDA required that a foreign-developed drug *must* be approved in another country, and then proceed to China for NDA/MAA submission. Even if there is MNCT data in China, the applicant had to wait for the CPP from the US, EU or other countries, and only then could there be a second submission (submission to CFDA to request clinical trial waiver). Under the new policy, there is no need for the CPP. After completing the MNCT and with relevant clinical study report (CSR), the sponsor can make an NDA/MAA submission to CFDA without CPP. This means, theoretically, China NDA/MAA submission and approval can be in parallel with (or even earlier than) foreign MAA approval.

These changes more closely align China to global standards, processes and timelines. They will have a deep and profound impact on the China local pharmaceutical market and on the global pharmaceutical industry. When this new policy takes effect, expected sometime in the second half of 2017, it promises to have a strong positive impact on foreign-developed new drug innovators who can have a full clinical development programme inside China, with significantly shortened regulatory review processes. The CFDA marketing authorisation approval can be in parallel with the US, EU or any other country's approval. We can expect more and more clinical trials to come to China and more foreign new drugs to be approved in China. The previous drug lag would be largely minimised. More foreign new drug investments are likely to come to China to set up new drug research centres, with an associated increase in activity for Chinese clinical trial sites and investigators and CROs in China.

With the movement toward a much shorter approval timeframe – previously, drug lag was often more than five years, but in the near future could be reduced to zero – the new drug innovator in China will need a stronger R&D team, with a global view, capable of high-quality and timely decision-making and actions.

Further, on 12 May 2017 CFDA announced four new policies to encourage innovation on drugs and medical devices: (1) Policy on reform of clinical trial management;¹² (2) Policy on acceleration of drug and medical device registration review process;¹³ (3) Policy on drug and medical device lifecycle management;¹⁴ and (4) Policy on protecting innovator's rights.¹⁵ All four of these new policies are under public consultation, with deadline of 10 June 2017 for response. Details of these policies are as follows:

Policy on reform of clinical trial management

- CFDA will no longer accredit clinical sites with good clinical practice (GCP). This opens clinical sites to all qualified hospitals, meaning a likely increase in the number of sites able to manage clinical trials in order to meet the need of increase of drug and medical device trials in China. CFDA retains responsibility for site inspections.
- Encourage social investment (non-government fund) to set up clinical trial sites to provide clinical trial service including active encouragement to hospitals, medical institutes and universities to provide clinical trial services.
IMPACT: Opens clinical trial market to all qualified hospitals and to social funds, creating increased capacity for clinical trials in China. Sponsor can sub-contract inspection or audit for sites to check if they are qualified.
- Improvement in ethics committee (EC) process and EC review efficiency. Each region (province) may set up a regional EC to guide EC activities and monitor trials and investigators in the region. Includes proposal for EC submission and approval to be prior to investigational new drug (IND)/CTA submission. For a multi-centre trial, after EC approval by the lead site, other sites can accept lead site's approval without repeating review.
IMPACT: With EC review before IND/CTA submission, CFDA/CDE reviewers will be able to review comments from sites, including those on trial design. This will encourage more active review of protocol by ECs.
- Improvement of clinical trial review process. A pre-submission consultation meeting between CFDA and sponsor will be requested for all Phase I or Phase III trial applications. If, after 60 working days following IND/CTA submission, there are no comments from CFDA/CDE, submission can be considered approved. Any substantial amendment for an ongoing trial must be submitted to CFDA in timely manner.
IMPACT: Improves communication channel for pre-submission consultation, aligning more closely with processes and timelines in ICH countries. Establishes more formality and process in the submission of substantial amendments after IND/CTA approval.
- Clinical trial data performed outside China, after on-site inspection by CFDA, can be used in China for registration, including BE study for generic drugs approved in the US, or EU or Japan.

Policy on acceleration of drug and medical device registration review process

- For drugs and medical devices indicated for serious life-threatening conditions or for significant unmet medical needs, where early- or mid-stage clinical data can predict clinical benefits, CFDA will be able to grant a conditional approval to allow early marketing in China, with a defined risk management plan and commitment to complete required clinical trial(s) based on CFDA's review and conclusion.
- China's Ministry of Health will issue a rare disease list for China and set up a rare disease patient registration process. The orphan drug and medical device manufacturer/applicant can apply for a clinical trial waiver or an agreed decrease in trial subject numbers. For orphan drugs or medical devices that are already approved outside China, CFDA can issue a conditional approval to allow marketing in China, while the sponsor completes commitment for clinical trial based on CFDA's review and conclusion.
- Stricter control of injectable formulations: injectable formulations

will not be approved if an oral formulation of same product already meets clinical needs.

- For active pharmaceutical ingredient (API), excipient and package material management: move from a specific approval process to a drug master file (DMF) process.
- Support for new drug to enter the market by encouraging hospitals to give priority to the purchase of new drugs that have established safety and efficacy data and a reasonable price. China Government will research the process for the maintenance of insurance drug list (drugs that can be covered by medical insurance), the price negotiation process (government negotiation with sponsor, in the meantime commitment to have the drug included in the insurance drug list), and support for the new drug to be included on the insurance drug list.

Policy on drug and medical device lifecycle management

- MAH system: The new MAH policy has been on trial in ten provinces since November 2015. The MAH holds all responsibilities for the drug regulatory, development and supply process, including nonclinical, clinical, manufacture, drug quality, marketing and delivery, clinical use and safety reporting. This policy will be rolled out across the whole of China in due course.
- Improving drug and medical device safety reporting system: The MAH is responsible for safety reporting, and should propose the actions to improve quality control, timely labelling change or other change initiated from safety analysis.
- Re-evaluation of marketed injectable drugs for safety, efficacy and quality control: This is consistent with the re-evaluation of generic drug quality and efficacy re-evaluation started in 2016. The purpose is to upgrade drug quality and remove low-quality products from the market.
- Re-evaluation of marketed medical device products: purpose is as above.
- Inspection system for whole regulatory, development and supply process: Nonclinical and clinical process will be inspected by CFDA; manufacturing process and quality control will be inspected by provincial-level FDA; sales and marketing processes will be inspected by city-level FDA.

Policy on protecting innovator's rights

- Setting up effective drug-patent-link system: every application for drug approval should include a statement on drug patent non-infringement. If an applicant is challenging another party's patent, the applicant should inform the patent-holder within 20 days after formal submission; the patent-holder should initiate any necessary legal action against the applicant within 20 days after being informed by the applicant and, in parallel, inform CFDA. CFDA can implement a waiting period of up to 24 months while any decision from a legal process is pending. If no legal decision has been given within 24 months, CFDA has the right to issue market approval to the applicant.
- Clinical trial data protection: An applicant can apply for a clinical trial data protection request, along with their NDA application – six-year protection for new drug, ten-year protection for new orphan drug or new paediatric drug, three-year protection for modified new orphan drug or new paediatric drug and ten-year protection for new biological products. The protection starts from the date of drug approval. Within this protection period, CFDA will not approve the same drug from different applicants.

In summary, these changes are a clear demonstration of CFDA's confidence to deepen ongoing reforms on the new drug evaluation and clinical trial process; to upgrade the drug (generic and injectable products) and medical device quality; to implement overall quality control on drugs and medical devices through R&D, manufacture, sales and marketing; and to protect the innovator's rights and patents.

Impact of the reforms

The reforms outlined in this article represent major positive changes for China's regulatory environment and are expected to better align the country with global regulatory norms by doing the following:

- **Shortening the new IND and NDA review timeline.** Increased human capacity at CDE will strengthen the standards for generic drugs, clinical trial requirements and the priority review process for innovative drugs, which is expected to resolve the current backlog. The CFDA's goal is for IND/CTA timelines to be around six months by the end of 2018 without any backlog.
- **Increasing transparency and globalisation.** CFDA is encouraging foreign sponsors to undertake global studies in China and recommending that local clinical sites join global studies to help ensure clinical trial data meet the requirements needed for China and global registration. This should overcome previous reluctance to include China in global studies or programmes because of the long IND timelines.
- **Incorporating stronger quality controls.** New requirements for generic drug quality and efficacy consistency evaluation and self-inspection of clinical data are being effectively enforced, which is anticipated to upgrade generic drug standards, clinical trial quality and clinical site GCP compliance. These may present some short-term challenges for generic pharmaceutical companies, but should be beneficial to new drug innovators planning to conduct meaningful, scientific trials, and should ensure that limited site resources are able to focus on such trials, which is a long-term, positive impact for the Chinese pharmaceutical industry.
- **Restructuring the pharmaceutical industry in China.** These reforms will have a profound and lasting impact on China's pharmaceutical industry. The industry currently is "big, but neither mature nor strong" and it is likely some of the manufacturers and their drugs will disappear over the next few years. However, there is a major incentive for innovative local companies to progress their efforts in new drug development.

This evolution is likely to provide stimulation for China's CRO industry. CFDA's self-investigation effort has resulted in 90 percent of 1,622 applications being withdrawn or rejected. Most local pharmaceutical companies use local CROs for generic BE studies with the top 19 CROs being from China.⁴ Local CROs face a major challenge to enhance their quality to meet the CFDA's stricter requirements. A critical indicator is that the expected budget for a BE study has been increased tenfold. Sponsors will be motivated to use reliable CROs with established standards to manage their trials and generate reliable data to meet requirements and support approval.

- **Minimising the drug lag.** Foreign drug registration process changed from "3-submission-3-approval" to "2-submission-2-approval" and eliminating CPP requirement make it possible that drug approval in China can be in parallel with the US or EU. AstraZeneca China announced on 24 March 2017 that Tagrisso (osimertinib AZD9291) obtained marketing approval from CFDA for non-small cell lung cancer (NSCLC) indication.¹⁶ This is a

clear example of the impact of CFDA's priority review process on a China NDA, since approval was granted only 16 months after approval from the US FDA on 13 November 2015, compared with the previous drug lag of typically three to five or more years. It is a demonstration of CFDA's strong intention to welcome global new drugs to meet Chinese patients' needs.

Conclusion

In line with the Chinese government's desire to modernise and improve a wide range of regulations, as well as to more closely align with established regulatory systems, these major reforms are expected to have a positive impact on China's healthcare system, the pharmaceutical industry and patients. The impact of these changes is already starting to become visible and is likely to be heavily tracked and reported over the coming months and years.

These are transformative changes; further reforms, with associated legislative and regulatory updates, can be anticipated over the next few months. Global companies with headquarters outside China need to familiarise themselves with these changes and their implications. Strong local China regulatory expertise remains essential to closely monitor these changes and ensure accurate and timely communication to all relevant stakeholders. In addition, a robust China regulatory strategy consultation or assessment will need to be prepared and agreed on much earlier than before in order to have a clear understanding of all the global scenarios. This should include any challenges, difficulties, benefits and advantages, which will enable a good understanding of how the China activities can be effectively integrated into the global programme.

The new framework and associated opportunities mean it is critical that clinical development and marketing plans have China integrated from the start, which is a new paradigm in the evolving global product development landscape.

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Note: All links above are to Chinese language webpages, with the exception of the final reference.

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