



FEATURE

The rewards of regulatory change

Launching innovative biopharma in China

David Xie, Xiaofeng Li and An Li

China's overhaul of regulations is giving hopeful biopharma manufacturers more than a foot in the door: a fast track to product approval. In this third of a four-article series, Deloitte compares your options and offers steps for competitive advantage.

CO-BUILDING, SHARING AND health for all' – this is the lofty vision of Healthy China 2030, the Chinese government's plan to achieve key health care goals in the next decade. A major pillar among them is establishing inclusive, health-improving regulatory systems, and there have been marked advancements already. But not all biopharma companies are adequately rising to the challenges – and opportunities – of China's new regulatory landscape. In Deloitte's view, the savvy executive will look to expand strategies for launching innovative new products by matching teams and development/approval options to capacity and need.

Reforms smooth the road to approval

For many years China's fast-developing life science and health care companies pushed for changes to how their industry is regulated. In August 2015 China's state council issued the 'Opinion on Reform of the Drug and Medical Device Approval System' (Document No. 44)¹, identifying several problems with drug and device registration. For example, foreign innovative drugs were delayed historically by an average of five to eight years before receiving approval in China, due mainly to the slow review process and additional local requirements.² This time that passes between a new drug's approval in a certain country after its approval in other jurisdictions is often referred to as drug lag.³

In response to Document No. 44, in recent years we have seen the China Food and Drug Administration (CFDA, later renamed to National Medical Product Administration)⁴ issue a series of regulatory reforms to address those concerns (see Figure 1). The main aims were to:

- improve the drug review process and shorten Investigational New Drug (IND) and New Drug Application (NDA) review timelines
- encourage new drug innovation

- accelerate market authorisation of medical innovations
- minimise drug lag.⁴

The reforms brought a fast-track approval process and a potential local-study waiver for products targeting rare diseases or diseases with substantial unmet needs.⁵ Since then, China has witnessed exponential growth in new approvals, and a significant reduction in drug lag as compared to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), as shown in Figure 2.

From drug approval trends to Priority Review Pathway

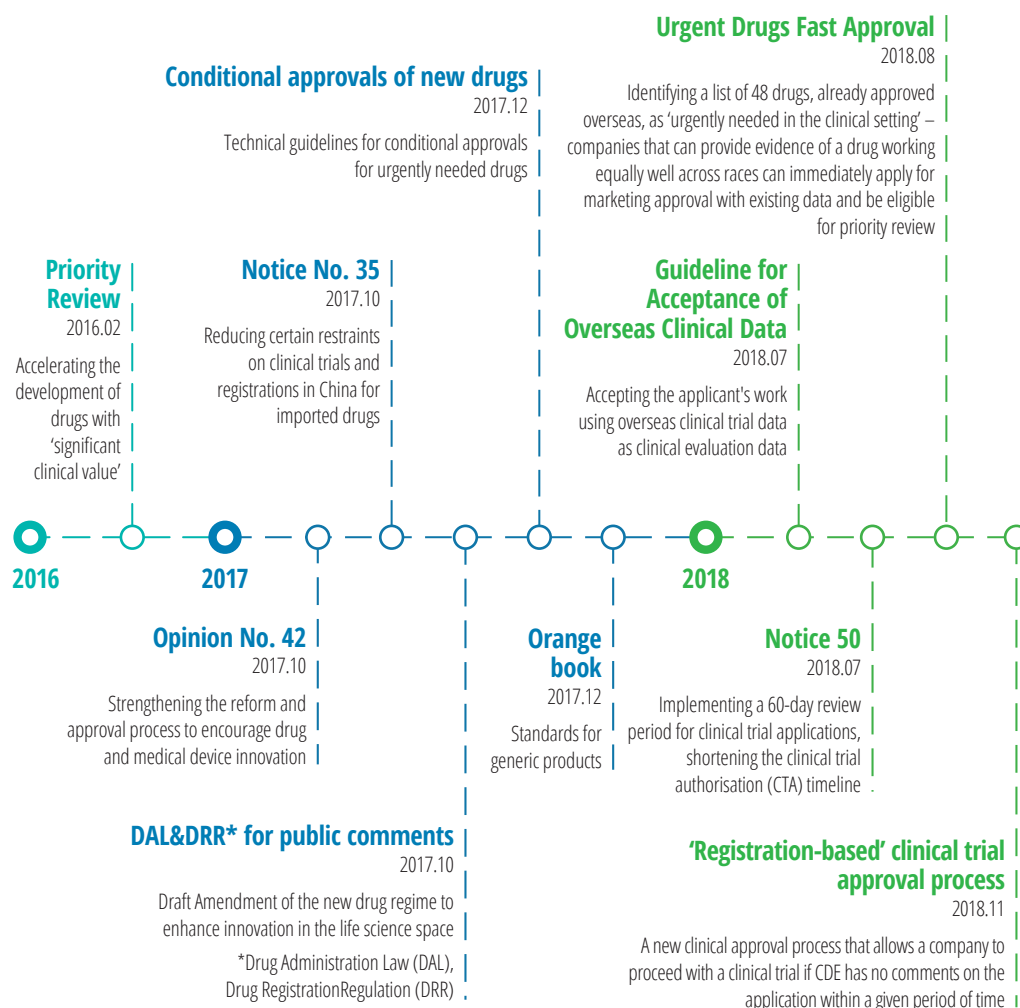
To bring marketed products up to international standards of efficacy, safety and quality, China made several efforts to improve the new drug approval process. First was to clear the registration-application backlog, resulting in significant acceleration of the review timeline.⁶ Second was the implementation of a 'Priority Review Pathway' to speed up the development of drugs with 'significant clinical value':⁷ novel drugs that treat severe or rare diseases, products in short supply, early generics, and drugs whose global clinical trial application in China parallels that in the US or EU, for example.

Products that fit into the priority review categories benefit from shortened regulatory timeframes throughout development and approval. Each of the timeframes is measured in days, with the single longest step taking 90 days. CFDA has given itself as few as five days to carry out certain tasks.⁸

A tsunami of new IND and NDA product launches has followed these reforms (see Figure 2). Consider that in 2016 only three multinational pharmaceutical company (MNC)⁹ drugs and two local drugs were approved. In 2017 that number increased by eight times, with 39 MNC drugs approved – a record high since the reformation. By the end of 2017, some 180 candidates had been granted priority review status,

FIGURE 1

Recent CFDA regulatory reforms to support innovative drugs



Source: Deloitte LLP, 2018.

according to CFDA.¹⁰ Some of them are included in the 2018 approval list, which totals 51 products. The surge of approvals is not expected to wane in the coming years; another 182 drugs were accepted for priority review during 2018.¹¹

In one example of fast approval with priority review status, a major MNC submitted its NDA for an investigational drug in early 2017. The drug's indication was for a serious condition in oncology, and approval was achieved in March 2017, with the drug reaching the market just one month later.¹² Domestic drugs have also benefited from the Priority Review Pathway. It took only ten days to approve a locally developed Ebola vaccine IND in 2017, although the approval was conditional on a commitment to

complete a Phase 3 trial later.⁹ This especially accelerated process indicates the positive impact of China's regulatory reforms on drug development, reducing approval timeframes and processes for INDs and NDAs.

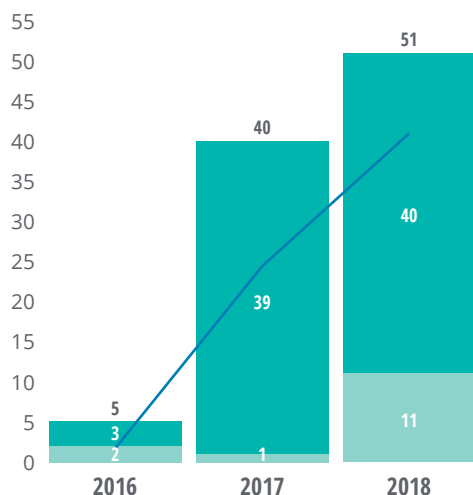
Along with fast approvals, the drug lag in China has diminished drastically in comparison to approvals in the US and EU. There are products that have received National Medical Products Administration approval within 12 months of being accepted by the EMA and FDA.⁸ On average, in 2017 China's approvals lagged behind the US and EU by 85 and 84 months, respectively; in 2018 the lag shrank to 28 and 31 months, respectively (see Figure 2).

FIGURE 2

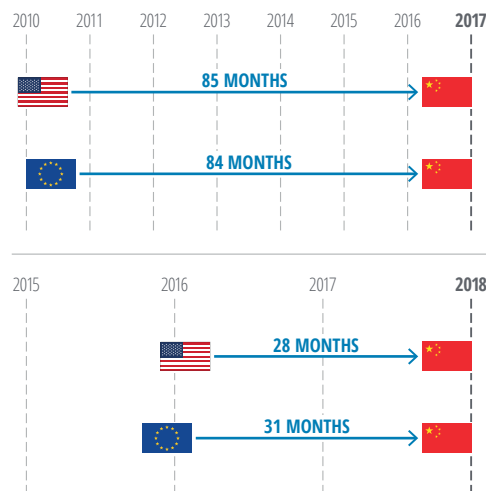
China's increase in number of new approvals and decrease in drug lag

Annual New Approvals in China

— Priority Review ■ MNC* ■ Local



Drug Lags Compared to FDA and EMA (in months)



*MNC: Multinational pharmaceutical company.
Source: Deloitte LLP, 2018.

The path less travelled: Alternatives for launch acceleration

The latest policies have opened the door to alternative regulatory processes for drugs addressing urgent unmet medical needs in China,¹¹ and the impact on the approval timeline is significant. Based on the urgency of an unmet need and the strength of a drug's clinical evidence, there are four types of alternative regulatory paths your launch team can take (see also Figure 3).

1. LOCAL MARKETING APPROVAL WITH CLINICAL TRIAL WAIVER

This is the fastest path, with approximately seven to eight months until NDA/IND approval. Only drugs with the potential to resolve very urgent unmet needs are given this priority: a) drugs that target orphan diseases or life-threatening diseases that have no effective treatment options on the market, and b) drugs already approved in the US, EU or Japan, or those very close to approval in these markets, that have sufficient Asian patient data demonstrating equivalence in efficacy and safety.

Drugs targeting rare diseases with life-changing effects will very likely benefit from this regulatory path before other kinds of drugs, although none have reportedly been approved this way yet. Only 121 rare diseases are recognised in China now¹³, compared with 6,000 to 8,000 recognised worldwide.¹⁴ As such, there is also a significant opportunity for manufacturers to actively foster the recognition of more rare diseases in China by working closely with leading clinical and public health expert.

2. LOCAL CONDITIONAL MARKETING APPROVAL

In this scenario, CFDA grants conditional marketing approval but may still require a manufacturer to conduct a local, large-scale study to provide long-term data. The average approval time is about ten months. Drugs fulfilling certain conditions are eligible: a) those for life-threatening or heavily debilitating diseases with no effective treatment options on the market, and b) those already approved in the US, EU or Japan, or very close to marketing approval in these markets but still lacking the long-term data required to fully demonstrate equivalent efficacy and safety among Asian patients.

Most of the drugs that have entered the approval process and qualify for conditional approval will already have started clinical studies in China. For example, several drugs targeting inflammation and immunology conditions, and appearing on the list of 48 ‘urgently needed’ drugs¹⁵ have been fast-tracked to the NDA review phase while manufacturers are still planning or conducting Phase 2/Phase 3 studies in China.¹⁶ Therefore, this model provides the best opportunity for drugs already in local clinical trials, given that the local data accumulated can be used to earn an early approval decision.

3. REDUCED LOCAL STUDY REQUIREMENT

Drugs that take this path still target relatively high unmet medical needs (for example, lack of a third line treatment for a specific tumour type) but have not yet been marketed globally. They also lack a statistically robust demonstration of evidence among Asian patients. Additionally, this alternative can be applied to drugs whose overseas clinical programmes have presented adverse events of concern, therefore requiring further local investigation.

For the approval process, the Centre for Drug Evaluation (CDE) will likely require a reduced local bridging study, instead of a full local registration

study. The local bridging study usually requires much less sampling and instead emphasises pharmacokinetics/pharmacodynamics (PK/PD) and major safety events. In 2018, certain oncology drugs - such as Certinib, a next-generation ALK+ drug for non-small cell lung cancer - were approved by the CDE in this way. Approval was based on a global international multicentre clinical trial (IMCT) (without China), combined with a local study with PK/PD as primary endpoints. This model is expected to gain in popularity.¹⁷

4. IMCT MODEL

The IMCT model is being widely practised by MNCs⁴. It ensures that China is involved in global registration efforts simultaneously with clinical trials, usually from Phase 2 (proof of concept) to Phase 3. This safest regulatory path is also the longest: 39 to 45 months are needed to approve a new drug, on average. The duration stems from the significant efforts necessary to coordinate between global and China studies, to ensure a high level of consistency in study requirements and executive strategies. This option may not be suitable for every disease/indication, given that the local CDE requirement and/or patient recruiting will likely be quite different from that on the global scale.

FIGURE 3

Alternative regulatory paths to accelerate launch, and their CDE evaluation criteria

TRIAL WAIVER

Path	Time	CDE Evaluation Criteria
<p>a</p> <p>NDA Submission</p> <p>1 month for pharma companies to prepare material</p> <p>NDA Approval</p> <p>6 months CDE to review</p> <p>?</p>	<p>7-8 months</p>	<ul style="list-style-type: none"> Assuming CDE considered the drug as orphan drug or recognised that the drug addresses unmet medical need in the treatment of life-threatening disease and with major clinical advance Overseas clinical trial data fully accepted Asian data in current clinical trial study is sufficient to demonstrate ethnic indifference
<p>b</p> <p>NDA Submission</p> <p>1 month for pharma companies to prepare material</p> <p>Conditional Approval</p> <p>6 months for CDE to review</p> <p>Post-launch Clinical Trial</p> <p>Time varies</p>	<p>10 months</p>	<ul style="list-style-type: none"> In addition to the criteria above, CFDA requires safety and efficacy data at larger scale for post-launch trial, usually within 5 years

NON WAIVER

<p>c</p> <p>CTA Submission</p> <p>1 month for pharma companies to prepare material</p> <p>CTA Review</p> <p>At most 3 months for CDE to review</p> <p>Bridging Study</p> <p>Time varies (about 11 months for PK study)</p> <p>NDA Submission</p> <p>1 month for pharma companies to prepare material</p> <p>NDA Approval</p> <p>7 months for CDE to review</p>	<p>24-27 months</p>	<ul style="list-style-type: none"> Overseas clinical trial data partially accepted CDE needs additional clinical trials to provide supplement data on PK, safety, efficacy or ethnic indifference based on the quality of overseas clinical trial data received
<p>d</p> <p>CTA Submission</p> <p>1 month for pharma companies to prepare material</p> <p>CTA Review</p> <p>At most 3 months for CDE to review</p> <p>Phase 3 study in China</p> <p>Time varies (about 24-30 months)</p> <p>NDA Submission</p> <p>1 month for pharma companies to prepare material</p> <p>NDA Approval</p> <p>7 months for CDE to review</p>	<p>39-45 months</p>	<ul style="list-style-type: none"> Overseas clinical trial data not accepted CDE requires a phase 3 clinical trial study in China to demonstrate drug efficacy on Chinese

Source: Gov.cn, NMPA Official Website, Expert Interviews, Monitor Deloitte Analysis.

Move forward: Seizing the opportunity from regulatory changes

The modified processes have ignited interest from biopharma companies in bringing innovative products to China – by presenting an increasingly appealing business opportunity. However, some companies have yet to update their strategy, continuing to view China as a ‘second-wave’ market in clinical/commercial programmes. These firms are losing competitive advantage, and should consider several strategic factors if they want to reap the opportunities that have opened up in recent years.

The process should start with having an active local regulatory/development team that will engage frequently with local authorities, assessing the chances of success down each regulatory path. With your team in place, work towards achieving the following goals.

1. GET A BETTER VIEW OF YOUR PIPELINE/PORTFOLIO

Multinational biopharma companies need to keep up with the recent regulatory changes while monitoring the progress of future changes. Equally important is to understand how the new regulations can be applied to your portfolio.

For innovative products in the early stages of development, revisit their portfolio and development programmes, and ask yourself: Have we missed any opportunities to capture value? To cope with China’s regulatory changes, companies need constantly to refresh their clinical development views related to China across various functions, and make a tailored plan on how to move forward there. In many cases, you will also need to adapt global plans to include China in first-wave markets, from development and commercial planning perspectives.

For innovative products closer to their launch, get regulatory and commercial teams to work together to find viable ways to accelerate the launch. Think comprehensively about patient need, regulations and market access. Then consider each of the four paths described above and their unique advantages, crafting a launch strategy that is tailored to your particular drug.

2. PAVE THE WAY FOR THE FUTURE REGULATORY PATH

The urgency and size of unmet medical needs play a key role in CDE evaluation, and it is difficult to evaluate comprehensively the clinical value of a product if the relevant disease is insufficiently studied. Compared to Western countries, China is still lacking a good characterisation of many diseases, such as related to epidemiology studies, unmet needs and disease burden. Particularly, there is a gap between knowledge of diseases regarding the Asian population cohort and more general knowledge. This affects biopharma companies’ ability to choose an appropriate regulatory path for their new innovative drugs.

Take a critical step to improving this situation by partnering with Key Opinion Leaders to bring disease-specific evidence and insights to the CDE discussion. Build those insights early and use them to try to evoke early influence (such as through study and publications), rather than waiting until the time of submission.

In other cases, China’s policies regarding rare disease remain nascent, meaning your regulatory team can work actively with government affairs and HEOR (health economics and outcomes research) teams to carry out an extended scale of study and to use the results to shape rare-disease policy. That kind of influence can speak volumes to a CDE evaluator who is trying to decide whether a product is worthy of going to market.

3. MERGE COMMERCIAL AND REGULATORY PLANS TO PREPARE FOR SUDDEN ACCELERATION

Deloitte has seen examples of biopharma companies being caught off guard by an accelerated launch without a commercial team to execute it. The prospect for acceleration in China is real, and biopharma executives looking for success in this new regulatory landscape should consider a broader market strategy.

Start your commercial planning early but keep it flexible enough to respond to various regulatory possibilities. Consider what constitute appropriate strategy and coordinated teams for your launch. Ideally, you will establish an internal system whose various teams – such as commercial, regulatory, global and local/country teams – work closely together toward a proper launch strategy.

GOING THE EXTRA MILE: CRAM FOR YOUR CDE PANEL TALKS

CDE panels play a deciding role in the approval process. It is important to prepare well for your open consultation with these panels by bringing the necessary materials, and even outside experts, to the discussion. These topics will likely be covered in the first round of discussions:

- **a.** epidemiology study data and ability to address unmet needs, preferably backed by Key Opinion Leader input and published data
- **b.** existing clinical trials data presentation, especially regarding Asian patients
- **c.** any future trial planned globally or in the Asia-Pacific region to further test safety
- **d.** long-term real world evidence data from mature markets, if available.



Conclusion

China's historical delay in drug approvals is a thing of the past, and the country looks toward 2030 with solid objectives for a more accessible and inclusive health care environment. No longer does a local study have to wait in the wings for a Phase 2 study outside China to conclude. Biopharma companies eyeing up China should set their sights on preparing an effective launch strategy. The CFDA's regulatory reforms, including fast-track approval and a local-study waiver for qualifying products, should be examined and exploited for launch success. Their benefits extend beyond the biopharma manufacturer to China's enormous population, which awaits the arrival of innovative new drugs.

Explore further insights into launching innovative biopharmaceuticals in China with three other articles in this series, on: market access and reimbursement, digital technologies and the changing health care environment.

Endnotes

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About the authors

DAVID XIE is a director based in Deloitte's Shanghai office. David has extensive R&D operations and strategy consulting experience. In his consulting career, David worked with various clients from the pharmaceutical, provider, private equity and not-for-profit fields, focusing on strategy and innovation projects as well as market access and organisational transformation, private equity investments and global health delivery.

XIAOFENG LI is a manager at Deloitte's Strategy Consulting practice and specialises in the life sciences and health care industry, focusing on commercial and clinical development as well as corporate strategy. He brings in-depth knowledge of health care systems in global markets as well as a high level of experience in delivering insights and solutions for a variety of complex strategic issues over a broad range of therapeutic areas.

AN LI is an analyst at Deloitte's Technology Consulting practice and specialises in the life sciences and health care industry, focusing on real world evidence, digital health care partnerships as well as corporate strategy. An's academic research experience additionally equips her with in-depth knowledge of health care systems in global markets.

Contacts

Thomas Croisier

Head of Monitor Deloitte France
Life Sciences Launch and Value Practice leader
Deloitte partner
Monitor Deloitte France
+33 1 58 37 92 87
tcroisier@deloitte.fr

Andrew Yu

Life Sciences and Health Care Consulting leader
Managing partner
Deloitte China
+86 21 23166913
andryu@deloitte.com.cn

David Xie

Director
Monitor Deloitte China
+86 21 61411209
daxie@deloitte.com.cn

Xiaofeng Li

Manager
Monitor Deloitte UK
+44 20 7007 3042
xiaofli@deloitte.co.uk

An Li

Analyst
Deloitte UK
+44 20 7303 5211
anxli@deloitte.co.uk

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