China's evolving regulatory landscape:
What are the opportunities and challenges?

China has made significant changes to its medicine regulatory system including:

Regulatory reforms

Regulatory reforms since 2015 have helped to **eliminate application backlogs, improve review timelines and increase approvals of innovative drugs**.

ICH

Involvement with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), first as a regulatory member in 2017 and then joining the Management Committee in 2018, has promoted **alignment with international standards and enhanced exchange and cooperation** with other regulatory and industry members.

Expedited pathways

Breakthrough, conditional, priority and special review pathways introduced in 2020 are supporting **accelerated development and approval of drugs with significant clinical value or for urgent health needs**.

But what do companies think of these changes?

This R&D Briefing summarises the findings of a study that examined CIRS member companies' perceptions of the evolving regulatory landscape in China, with the aim to identify current challenges and opportunities for improvement.

Key findings

The impact of recent regulatory changes on medicine development, regulatory review and life cycle management has generally been positive, but changes are still needed:

- **Greater harmonisation of Chinese regulatory framework with international standards**
- **Optimise Human Genetic Resource Regulation process and requirements**
- **Align drug application classification**
- **Increase transparency and timeliness of processes and enhance communication with industry**
- **Improve support for innovative products**

R&D BRIEFING 84

CIRS Centre for Innovation in Regulatory Science

Background

Over the last decade, a number of reforms have taken place in China with respect to medicine registration. These have aimed to address the backlog in drug registrations and encourage the research and development of new drugs by introducing and promoting innovative approaches, such as the use of facilitated regulatory pathways. The implemented changes have not only allowed China to increasingly participate in simultaneous global development but have also led to faster approvals of medicines for Chinese patients (Figure 1).

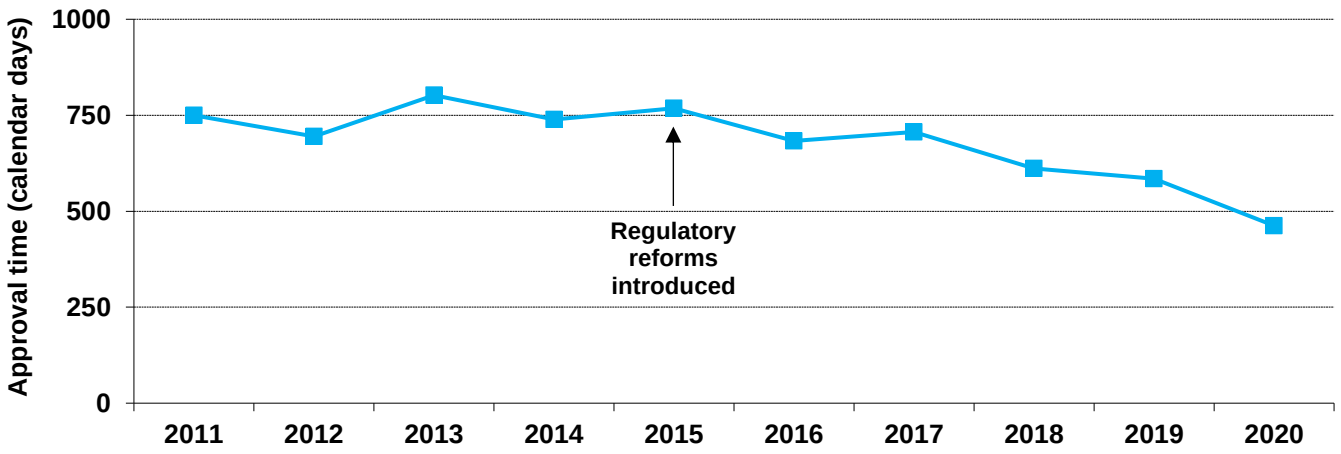


Figure 1: Fall in regulatory approval times in China for New Active Substances

Source: CIRS Industry Metrics Programme. The total number of NASs is 95 and the total number of companies is 14. Approval times shown are three-year averages with the exception of 2020, which is a two-year average.

CIRS has been monitoring these changes and supporting advocacy efforts in several ways. The first is through its industry Metrics Programme, which assesses elements specific to China, such as investigational new drug application timing and use of data from multi-regional clinical trials (MRCT), as well as comparing the time from first world submission to submission in China alongside other agencies globally. In addition, CIRS conducted a special study on this topic in 2015, based on the many procedural changes that occurred then. More recently, CIRS has been working with the National Medical Products Administration's (NMPA's) Centre for Drug Evaluation (CDE), which is now represented on the CIRS Scientific Advisory Council (SAC) to identify areas of mutual interest.

Although CIRS continues to monitor China through its annual industry metrics study, feedback from participants of the study suggested that China requires "a different approach considering the fast changes in the environment". CIRS therefore conducted an in-depth survey of its member companies to evaluate the evolving regulatory landscape in China, including the challenges and opportunities to ensuring timely availability of medicines in China.

Methods & overall perceptions

Methods

A two-part survey was sent out in October 2021 to 21 major international pharmaceutical companies who were members of the CIRS Regulatory and Access Programme. The first part of the survey assessed the impact recent policy changes have had on medicine development, review and life cycle management within China, as well as how these areas could evolve in future. The second part of the survey asked respondents to suggest three process, guideline or policy changes that they would like to see in China to enable the development, review and life cycle management of new medicines.

Survey responses were aggregated to give an overview of current company perceptions of China's regulatory environment. Responses were included irrespective of whether the respondent had experience of licensing a New Active Substance (NAS) in China or not. If a respondent answered 'Not sure' when asked about the impact of a particular area, this was excluded from the final analysis i.e. 'Not sure' results are not shown.

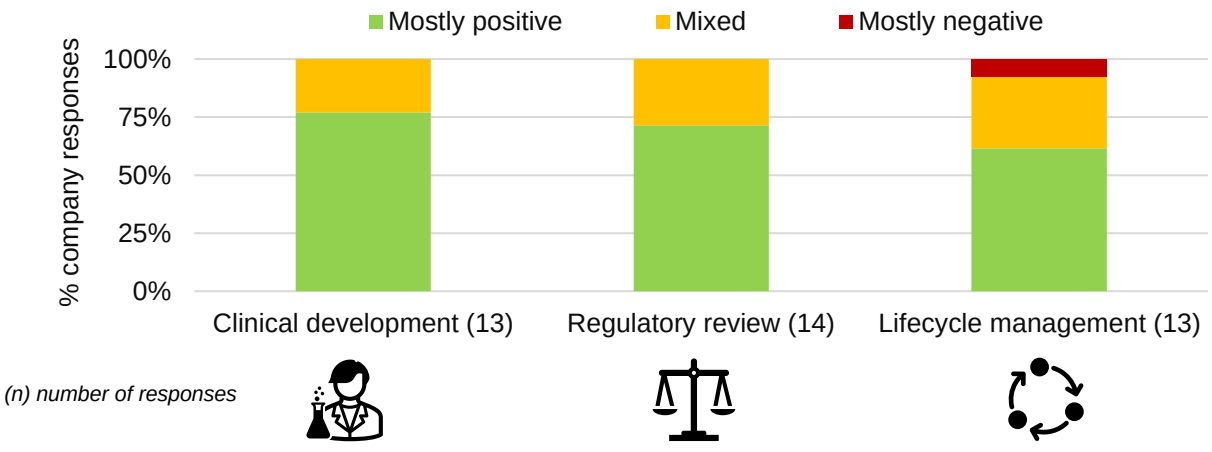
Response rate and characteristics of respondents

14 companies responded to the survey in November 2021, 93% of which monitored the landscape in China through regulatory intelligence. 86% of respondents had experience of scientific interactions with NMPA's Centre for Drug Evaluation (CDE) and 64% had NASs in development that would be submitted for licensing in China. 64% had received approvals for NASs in China and 21% had NAS applications rejected or withdrawn in China over the last 12 months.

Overall perception of the impact of regulatory policy changes in China

In general, the majority of companies thought that recent regulatory policy changes in China had a positive impact on medicine development, review and life cycle management processes over the last 12 months (Figure 2). Perceptions of these three areas are explored in more detail in the next sections.

Figure 2: Company perceptions of the impact of regulatory policy changes in China over the last 12 months

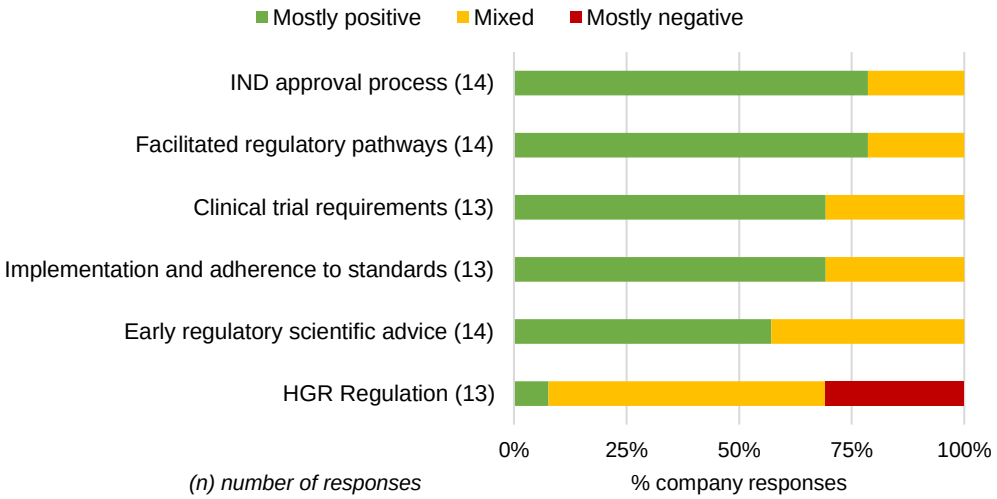


Impact of recent changes on clinical development

When asked about the impact that different areas/steps of the clinical development process in China were having on R&D, the majority of companies responded positively (Figure 3). The Investigational New Drug (IND) approval process was reported to have a predictable three-month timeline. Efforts to achieve simultaneous R&D and registration were seen as positive, though the need for China to be included in multi-regional clinical trials remained a barrier. Facilitated regulatory pathways, such as Breakthrough Therapy Designation (BTD) and conditional approval, were seen to have clear criteria, processes and timelines and had improved communication between companies and NMPA. While NMPA becoming a member of ICH was seen as having a positive impact on the implementation of international standards in China, it was thought that adherence to some of these standards was lacking. There was limited experience of using scientific advice in China; it was noted that communication mechanisms had improved but sometimes the feedback obtained was not specific enough.

In contrast, the Human Genetic Resource (HGR) Regulation was seen by most companies as having a mixed impact on clinical development in China. HGR approval was reported to be the main rate limiting step in the start-up of clinical studies, adding approximately six months to development timelines. However, some companies reported that the HGR office in China was becoming more open and flexible and that the HGR approval rate was increasing.

Figure 3: Company perceptions of the impact of different areas/steps of the clinical development process in China



Suggestions to evolve each of these areas to improve predictability, transparency and timeliness are shown in Table 1 below.

Area	Suggestions to evolve this area
IND approval process	• Reduce local requirements e.g., for Chemistry Manufacturing Control (CMC) documents • More alignment with ICH Guidelines e.g., M1 • Reduce timelines from 3 months to 1-2 months
Facilitated regulatory pathways	• Increase uptake of designations by aligning with global standards, improving transparency e.g., reasons for rejections, and implementing risk-based approaches to CMC • Participate in work sharing initiatives e.g., Project Orbis, Access Consortium • Develop rare disease policies
Clinical trial requirements	• More alignment with ICH E17 (MRCT) • Reduce local requirements e.g., CMC • Develop more supporting measures to facilitate the acceptance of MRCT and overseas data
Implementation and adherence to standards	• More alignment with ICH Guidelines e.g. manufacturing docs, pooling strategy, pharmacopoeia • Continue pursuing Pharmaceutical Inspection Co-operation Scheme (PIC/S) membership • Develop supporting documents and conduct training to ensure adherence
Early regulatory scientific advice	• Increase opportunities for early interactions • Improve capacity and capability for providing scientific advice • Reduce dossier requirements for pre-IND meetings
HGR Regulation	• Standardise and simplify the HGR approval process and clarify requirements – explore the possibility for application submission to occur prior to ethics committee/clinical trial application approval • Enhance communication channels with industry • Give more clarity on data ownership and sample export

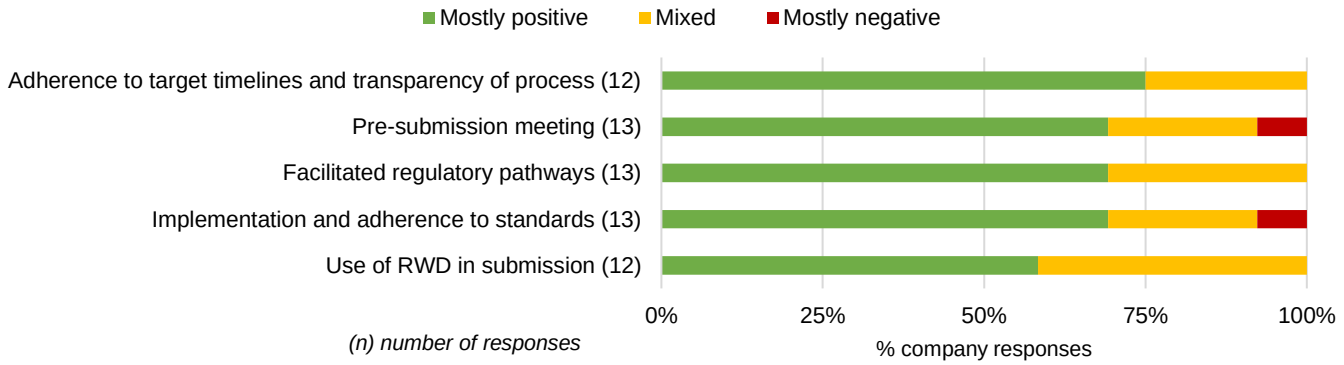
Table 1: Company suggestions to improve different areas of the clinical development process for NASs in China

Impact of recent changes on the regulatory review process

When asked about the impact that different areas/steps of the regulatory review process in China were having on the registration of NASs, the majority of companies responded positively (Figure 4). Respondents reported that the Drug Registration Regulation had clarified target timelines for each step of review, but there was still a lack of predictability as no overall timeline or target decision dates were given, and communication during review was sometimes challenging. Facilitated regulatory pathways such as priority review and conditional approval were generally seen positively, in that they had clear guidelines and had reduced review timelines by 4-5 months. Priority review was reported to have become narrower in criteria/scope, which some respondents viewed negatively, while others felt this was positive as it would allow the Chinese agency to focus more on valuable clinical products. Nevertheless, it was noted that more could be done to reduce timelines for priority review.

Although pre-submission meetings, such as pre-New Drug Application (NDA) meetings, were seen by respondents as generally useful, it was noted that CDE had limited resource to conduct these meetings and that the advice given was not always consistent e.g. across therapeutic areas. As in clinical development, respondents reported that the implementation of international standards in the review process was improving, but adherence to these standards was sometimes lacking. When asked about the use of real-world data (RWD) in submissions, there were mixed responses; the Chinese agency was seen to have taken positive steps by issuing guidelines and being more open to using RWD, however, this was not necessarily translating into acceptance of RWD.

Figure 4: Company perceptions of the impact of different areas/steps of the regulatory review process in China



Other positive developments that were reported were the parallel process for CDE review, quality control testing and pre-approval inspections, as well as the ability to track applications and review reports on the CDE website. Suggestions to evolve each of the different areas to improve predictability, transparency and timeliness are shown in Table 2 below.

Area	Suggestions to evolve this area
Adherence to target timelines and transparency of process	• Communicate overall target review timeline, including all steps • Enhance internal collaboration and external communication during the review
Pre-submission meeting	• Provide more clarity on the process and timelines for pre-submission meetings • Increase capacity for pre-submission meetings
Facilitated regulatory pathways	• Further reduce the priority review timeline • Develop more detailed guidance on facilitated regulatory pathways • Create additional pathways e.g., for rare disease
Implementation and adherence to standards	• Reduce regional requirements • More alignment with global standards e.g., ICH M8 (electronic Common Technical Document)
Use of RWD in submission	• Expand existing guidelines on RWD • Build experience to enable routine acceptance of RWD for applications (first approval and post-approval settings)

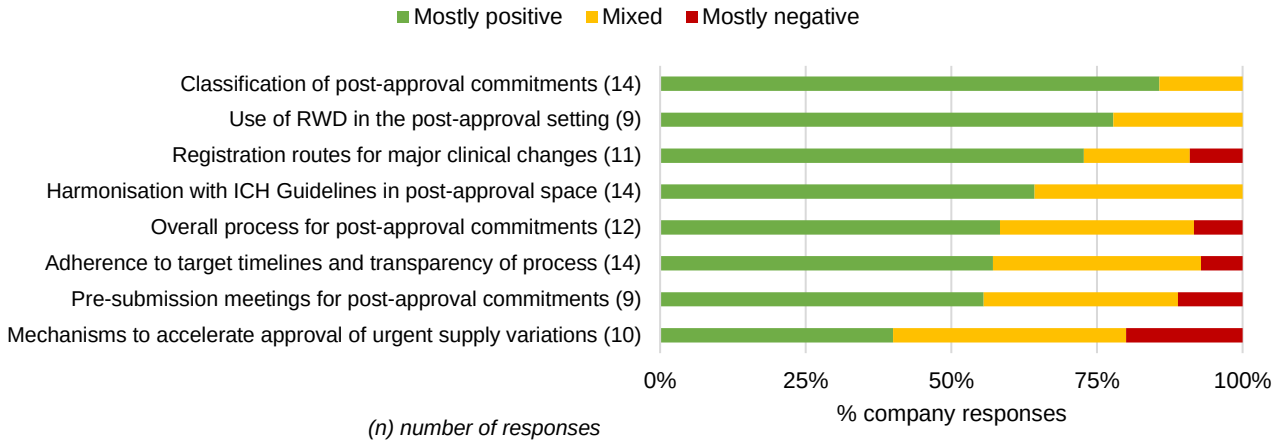
Table 2: Company suggestions to improve different areas of the review process for NASs in China

Impact of recent changes on life cycle management

When asked about the impact of life cycle management for medicines in China, the responses were generally positive but with slightly more variation than for clinical development and review (Figure 5). The classification of post-approval changes in China was described as well-defined and in line with the US FDA, and it was noted that the use of RWD in the post-approval setting was being encouraged. As in clinical development and regulatory review, respondents reported that the implementation of international standards in the post-approval setting was improving, but adherence to these standards was sometimes lacking.

In general, transparency and adherence to target timelines were found to be good, though the procedure and standards for life cycle management were sometimes felt to be unclear. It was also noted that pre-submission consultation meetings for post-approval commitments had an unclear process with long timelines. The most hindering barrier was felt to be the lack of mechanism to accelerate approvals of urgent supply variations; this was thought to add 3-6 months to the post-approval process.

Figure 5: Company perceptions of the impact of different areas/steps on life cycle management in China



(n) number of responses

Suggestions to evolve each of the different areas of medicine life cycle management are shown in Table 3 below.

Area	Suggestions to evolve this area
Classification of post-approval changes	• Develop and implement guidelines on post-approval changes
Use of RWD in the post-approval setting	• Develop and implement guidelines on RWD • Accept RWD routinely in applications
Registration routes for major clinical changes	• Changes to legislation needed • Expedited pathway for variations
Harmonisation with ICH Guidelines in post-approval space	• Continue aligning with ICH Guidelines e.g., M4Q (Common Technical Document – Quality section), Q12 (Life cycle management) • Align CMC guidelines • Reduce quality control testing • Align pharmacopeia with internationally recognised pharmacopoeia or ICH Q4A-Q4B (Pharmacopoeias)
Overall process for post-approval commitments	• Develop supporting guidelines to have clearer procedures and standards for post-approval commitments • Encourage completion of post-approval commitments e.g., data protection
Adherence to target timelines and transparency of process	• Set predictable and reasonable timelines • Implement risk-based approaches
Pre-submission consultation meetings for post-approval commitments	• Develop more specific guidance on post-approval commitments • Improve quality of communication with sponsors
Mechanisms to accelerate the approval for urgent supply variations	• Develop a formal mechanism for approving urgent supply variations • Build on experience from urgent variations for COVID-19 related products

Table 3: Company suggestions to improve different areas of life cycle management in China

Opportunities for improvement

Respondents were asked to suggest their top three process, guideline or policy changes needed to enable the development, review and life cycle management of new medicines in China. These suggestions are summarised in Table 4 below.

Change	How to achieve
Greater harmonisation of Chinese regulatory framework with international standards	• Provide clear guidance and limit local requirements • Continue implementing ICH Guidelines, PIC/S standards and adopt World Health Organisation (WHO) Good Regulatory Practices • Participate in work-sharing approaches to build trust • Invest in training and increase cooperation with industry
Optimise, standardise and simplify HGR process and requirements	• Better transparency of requirements and review/approval process • Enhance communication mechanism with industry • Clarify requirements around data ownership and sample export
Align drug application classification	• Classification should be based on degree of innovation • Implement a “New drug” definition aligned with international standards • Develop guidelines for data protection and patent extension • Legislation around classification could be revised
Increase transparency and timeliness of processes and enhance communication with industry	• Need clearer guidance from CDE • Improve capacity for meetings with sponsors e.g., pre-IND, pre-NDA • Build experience and capability to ensure high-quality communication for advice meetings
Support for innovative products	• Introduction of new regulation e.g., for rare diseases • Improving technical support for rare disease drugs, paediatric drugs, advanced therapy medicinal products (ATMPs), blood products, etc., but also improving access to these products.

Table 4: Changes that companies would like to see implemented in the China regulatory system

Next steps

CIRS will continue monitoring the regulatory landscape in China by:

- Industry benchmarking of submission and review timelines through its Metrics Programme
- Assessing the agency by measuring its process and review timelines
- Investigating new ways of working, in particular for ATMPs, digital health technologies and RWD

CIRS will also continue promoting regulatory science in China to ultimately improve decision making in both companies and agencies.

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and Health Technology Assessment (HTA) policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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