China Reform of the Regulatory Environment

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## Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BE</td>
<td>Bioequivalence</td>
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<tr>
<td>CDE</td>
<td>Center for Drug Evaluation</td>
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<td>CFDA</td>
<td>Chinese Food and Drug Administration (old name of NMPA)</td>
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<td>CMDE</td>
<td>Center for Medical Device Evaluation, NMPA</td>
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<td>CPP</td>
<td>Certificate of Pharmaceutical Product</td>
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<tr>
<td>CRO</td>
<td>Contract Research Organisation</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FIH</td>
<td>First in-human</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>GQCE</td>
<td>Generic drug quality and efficacy consistency Evaluation</td>
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<td>HGRAC</td>
<td>Human Genetic Resource Administration of China</td>
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<tr>
<td>ICH</td>
<td>International Council for Harmonisation</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug</td>
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<td>MA</td>
<td>Marketing Authorisation</td>
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<td>MAA</td>
<td>Marketing Authorization Application</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorization Holder</td>
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<tr>
<td>NDA</td>
<td>New Drug Application</td>
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<tr>
<td>NHC</td>
<td>National Health Committee</td>
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<tr>
<td>NMPA</td>
<td>National Medical Products Administration (formerly CFDA)</td>
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<tr>
<td>NPC</td>
<td>National People’s Congress</td>
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<tr>
<td>U.S.</td>
<td>United States</td>
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<tr>
<td>VAT</td>
<td>Value added tax</td>
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Background

China is currently the second largest pharmaceutical market in the world and was estimated in 2017 to be worth $122.6 billion. It was also the biggest emerging market for pharmaceuticals, with growth tipped to reach between $145 billion and $175 billion by 2022.¹

Due to its high potential for growth, China has also become one of the most important regions for global drug development, but historically the regulatory environment in China was considered highly challenging for the following reasons:

• The Chinese drug registration process differs from that in many other countries, in that new drug applications (NDAs) for all imported drugs, whether marketed overseas or not, are required to include data from local clinical trials;
• Major differences exist between international standards and some local products and manufacturers as far as quality is concerned;
• The time frame for review and approval of new drugs is longer than for most major countries;
• A lack of capacity in the regulatory body has resulted in a backlog of applications.

In August 2015, the China State Council released “Opinions on Reforming the Review and Approval System for Drugs and Medical Devices.” The intention of this reform was to promote a structural change and upgrade of the pharmaceutical industry and bring products already marketed in China up to international standards in terms of efficacy, safety and quality. These reforms have aimed to:

• Eliminate the existing backlog of registration applications
• Establish an environment for maximising the quality of generic drugs
• Create a framework in China that encourages research and development of new drugs in line with global development
• Improve the quality and increase the transparency of the review and approval process

China has a large pharmaceutical industry; it is estimated that there are between 4,500 and 6,000 manufacturers,² with businesses based on generics, active pharmaceutical ingredients or traditional Chinese medicine. Most of the manufacturers are small- or medium-sized enterprises. There are, however, many manufacturing sites in China that meet global Good Manufacturing Practice (GMP) standards. Previous regulations meant that the Marketing Authorisation Holder (MAH) also had to be the owner of the manufacturing site. The reform has seen the separation of the activities of the MAH and the manufacturer; thus, the environment is now more flexible, allowing research companies to hold the Marketing Authorisation (MA) while contracting out the product’s manufacture to a third party.

Generic drugs available in China tend to have several approved manufacturers, and there is a sparsity of official guidance for the generics industry. The China Food and Drug Administration (CFDA)* has published “restricted” and “promoted” categories of generic drugs, suggesting that a more sound control and guidance of the generics industry is expected.

As there has traditionally been stiff competition in the generics arena, local Chinese companies have not been interested in developing innovative new drugs, and their current capacity for such development is low. In the recent past, these companies have relied on bioequivalence (BE) trials for generic drug registration, but with CFDA’s new requirements, they will need to start focusing on generic quality and efficacy. As such, any data considered inaccurate or incomplete will not be accepted, creating the potential for existing licenses to be withdrawn.

* CFDA became NMPA (National Medical Products Administration) in 2018. CFDA has been used in this document to relate to any guidance or procedure that predates the 2018 reforms.
## Reform Impacts: 2016

### Table A: Reforms 2016

<table>
<thead>
<tr>
<th>Reform</th>
<th>Detail/Opportunity</th>
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<tr>
<td>Self-inspection of clinical data</td>
<td>CFDA announced a self-inspection programme for clinical data; this required MA applicants, contract research organisations (CROs) and clinical sites to self-inspect. More than 1,600 applications were pending approval. This initiative began in July 2015 and uncovered fake and incomplete data, which resulted in non-approvals and, in some cases, investigations by CFDA. CFDA used its experts to inspect selected studies that were suspicious in terms of data authenticity. For future NDAs, CFDA requires applicants to include a clinical trial self-inspection report, which CFDA will review. After 12 months, CFDA reported that around 90 percent of the backlogged applications had been withdrawn by applicants or rejected by CFDA.</td>
</tr>
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</table>
| Priority review           | In February 2016, CFDA announced a new ‘priority review’ process to encourage 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 U.S., EU, Japan and other countries. An updated version was published in 2017. ‘Priority review’ status can be requested based on the following criteria:  
  - Innovative drug that is not approved anywhere worldwide  
  - Innovative drug where the manufacturing is to be transferred to a site in China  
  - Global clinical trial application to China in parallel with the U.S. or EU  
  - The innovative drug is for HIV/AIDS, viral hepatitis, a rare disease(s), for malignant tumours and for paediatric indications  
  - The product is a newly launched generic drug |
Table A: Reforms 2016 (continued)

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<th>Reform</th>
<th>Detail/Opportunity</th>
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<tbody>
<tr>
<td>Priority review (continued)</td>
<td>Positive ‘priority review’ status provides applicants with priority reviewer resources allocated by the Center for Drug Evaluation (CDE) and priority communication pathways to obtain advice and expedited feedback from the CDE/CFDA. CFDA considers that the target approval time for a priority review, from submission, is six months or less; however, this is not yet being seen consistently. The target seems to have worked well for applications submitted after February 2016. • On 28 December 2017, NMPA updated opinions on priority review with two modifications in the scope, which are in line with State Council “Opinions of Deepening the Reform of the Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices.”6 NDAs with clinical trials performed by the National Clinical Medical Research Center and confirmed by CDE's management department shall be given priority review and approval • Under the circumstances in which there is a major threat to the public health, registration applications for drugs that have been granted compulsory licensing shall be given priority review and approval. The specific circumstances under which there is a major threat to the public health and the specific procedures for initiating compulsory licensing shall be promulgated separately by the National Health and Family Planning Commission together with relevant authorities.</td>
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<td>Additional capacity at CDE</td>
<td>In 2015 there were around only 70 reviewers to handle an annual load of more than 7,000 drug applications in CDE. Following a new hiring exercise, 600 new drug reviewers were in place by the end of 2016.4 Additional hiring of reviewers has continued in 2017 and 2018.</td>
</tr>
<tr>
<td>Marketing Authorisation Holder rationalisation/new classification/definition of new drugs</td>
<td>MAH system reform ensures that drug research and development institutions can obtain and hold MAs without needing to own the manufacturing site.7 • 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 • Major incentive for local new drug innovators in China, who can now hold MAs independently • Reform implemented in a phased manner starting with a trial in 10 selected provinces, mostly on China’s east coast, over three years • Encourages drug researchers/institutions to focus on research and development and alleviates the need to invest in their own manufacturing plants Creation of a new classification of drug, “new to the world,” to replace the previous “new to China” category.8 • Based on the global MA approval status and the location of the manufacturing site(s) (inside or outside China) • Removes the previous definitions that were based on the specific status in China, and aligns classification more closely to other regulatory agencies</td>
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Table A: Reforms 2016 (continued)

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<tr>
<td>Generic drug quality and efficacy consistency Evaluation (GQCE)</td>
<td>Generic drug manufacturers are required to start drug consistency research on quality and efficacy; target completion date by the end of 2018.⁹ A product list has been developed by CFDA that lists which generic drugs need this consistency evaluation. For evaluation purposes, the comparator product is the “innovator drug,” or a globally recognised similar drug. “Innovator drug” means the first globally marketed drug with the full data package to support its safety and efficacy.</td>
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Reform Impacts: 2017

On 17 March 2017, CFDA announced its decision to change the requirement on imported drug registration. The changes are to encourage foreign-developed new drugs to undergo clinical investigation within China and outside China in parallel, with the intention to shorten the time period between approval outside China and approval inside China to meet the need for new drugs for Chinese patients.

These changes bring China more into line with global standards, processes and timelines. It is expected that the new policy will have a positive impact on ex-China sponsors who can develop a full clinical development program inside China, with significantly shortened regulatory review processes. The CFDA marketing authorisation approval can be in parallel with the U.S., EU or any other country’s approval.

It is envisaged that more foreign (ex-China) sponsors will want to conduct research in China, and more foreign new drugs are likely to be approved. There is hope that the changes will encourage foreign sponsors to invest in China and set up new drug research centers, with an associated increase in activity for Chinese clinical trial sites and investigators and potentially CROs in China.

Key changes in 2017 are shown in the table below.

Table B: Reforms 2017

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<tr>
<th>Reform</th>
<th>Detail/Opportunity</th>
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<tr>
<td>Opening up of first-in-human (FIH) Phase I trials to global development</td>
<td>This means that for new chemical drugs and new therapeutic biological products, foreign applicants can have a full clinical development plan executed inside China in parallel with the global development programme.¹⁰ This change effectively opens an FIH Phase I market in China.</td>
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Note: Preventative vaccines still may not undergo a global trial inside China.
Table B: Reforms 2017 (continued)

<table>
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<th>Detail/Opportunity</th>
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| Simplified process for gaining a marketing approval | Previously, foreign-developed new drugs needed three submissions:  
• Multinational clinical trial submission to request global Phase II or III trial in China  
• After the drug had been approved in U.S. or EU and a certificate of pharmaceutical product (CPP) was available, submission to CFDA to request clinical trial waiver (requesting exemption from need to do any additional local trials)  
• NDA submission to CFDA for market approval  
Under the new policy, there is no need for the second submission (clinical trial waiver) and the sponsor can move directly to the NDA submission.  
This simplified process could shorten the whole approval process by about one year. |
| Clinical trial management\(^\text{11}\) | CFDA will no longer accredit clinical sites with Good Clinical Practice (GCP).  
• Opens up potential for clinical sites in all qualified hospitals  
• Likely increase in the number of sites able to manage clinical trials  
• CFDA retains responsibility for site inspections  
Opens clinical trial market to all qualified hospitals and to social funds, creating increased capacity for clinical trials in China.  
Sponsor can subcontract inspection or audit for sites to check if they are qualified.  
• Opportunities for CRO QA departments to expand to take on extra work  
Improvement in Ethics Committee (EC) process and review  
• Each region or 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 prior to investigational new drug (IND) submission to CFDA/CDE  
• For a multicentre trial, after EC approval by the lead site, other sites can accept the lead site’s approval without repeating review  
• With EC review before IND submission, CFDA/CDE reviewers will be able to review comments from sites, including trial design comments, encouraging a more active review of protocol by ECs  
Improvement in the clinical trial/IND review process means a presubmission consultation meeting between CFDA and the sponsor will be required for all Phase I or Phase III trial applications. If after 60 working days following submission, there are no comments from CFDA/CDE, the submission can be considered approved. Any substantial amendment for an ongoing trial must be submitted to CFDA in a timely manner.  
• Potential for CRO regulatory affairs functions to expand to coordinate/lead meetings  
Clinical trial data from studies outside China can be used in China for registration, including any BE studies for generic drugs approved in the U.S., EU or Japan. These studies will be subject to an on-site inspection by CFDA. |
Table B: Reforms 2017 *(continued)*

<table>
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| **Acceleration of drug and medical device registration review process**<sup>11</sup> | For drugs and medical devices that are indicated for serious life-threatening conditions or for significant unmet medical needs, where early- or mid-stage clinical data predicts outstanding clinical benefit, CFDA can grant a conditional approval to allow early marketing in China. The conditional approval requires an approved risk management plan and a commitment to complete required clinical trial(s) based on CFDA’s review and conclusion, much the same as is currently the norm in the EU. China’s Ministry of Health issued a Rare Disease list for China (see 2018 section) 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(s) based on CFDA’s review and conclusion  

  Stricter controls on injectable formulations mean that they will not be approved if an oral formulation of the same product already meets clinical needs.  
  Active pharmaceutical ingredient, excipient and package material management moves from a specific approval process to a drug master-file process.  
  • Brings the process in line with the majority of the rest of the world  

  Support for new drugs to enter the market by encouraging hospitals to give priority to the purchase of new drugs that have established safety and efficacy data at a reasonable price.  
  • The Chinese government is looking for a process for maintaining an insurance drug list following price negotiation with the sponsor, but in the meantime they have committed to have new drugs included on the insurance drug list |
| **Drug and medical device life cycle management**<sup>11</sup> | The new MAH policy has been on trial in 10 provinces since November 2015.  
  • The MAH holds all responsibilities for the drug development, regulatory and supply process, including nonclinical, clinical, manufacture, drug quality, marketing and delivery, clinical use and safety reporting  
  • 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 is consistent with the re-evaluation of generic drug quality and efficacy started in 2016. The purpose is to upgrade drug quality and remove low-quality products from the market. The same exercise is ongoing for medical devices  
  • An inspection system for the entire drug development, regulatory and supply process will be put in place. Nonclinical and clinical processes will be inspected by CFDA; the manufacturing process and quality control will be inspected by provincial-level FDA; sales and marketing processes will be inspected by city-level FDA |
### Table B: Reforms 2017 (continued)

<table>
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| Protecting innovators’ rights¹¹ | Establishment of an effective drug-patent system  
  • Every application for drug approval will include a statement on drug patent noninfringement  
  • 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 the new MA  
  Clinical trial data protection  
  • An applicant can apply for a clinical trial data protection request, along with the NDA  
  • Six-year protection for new drug, 10-year protection for new orphan drug or new paediatric drug, three-year protection for modified orphan drug or paediatric drug and 10-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 |

### Reform Impacts: 2018

Note: CFDA became National Medical Products Administration (NMPA) in 2018.

### Table C: Reforms 2018

<table>
<thead>
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<th>Detail/Opportunity</th>
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| NHC Rare Disease list                                                                           | The National Health Committee issued the first batch list of Rare Diseases on 11 May 2018.  
  • The list is attached as a PDF below: Note this is in Chinese, with a bilingual disease list.                                                                                                                                         |
<p>| NMPA elected member of ICH Management Committee                                                  | On 7 June 2018, NMPA issued a notice saying that at the first meeting of the International Conference on Technical Registration of Human Drugs in Kobe, Japan, NMPA was elected as a member of the International Council for Harmonisation (ICH) Management Committee.¹² |</p>
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| Technical Guideline for Acceptance of Overseas Drug Clinical Trial Data (No. 52) | On 10 July 2018, NMPA released the final version of “Technical Guideline for Acceptance of Overseas Drug Clinical Trial Data.”
  - As per the Basic Principles for Acceptance of Overseas Clinical Trial Data, applicants should ensure the authenticity, integrity, accuracy and traceability of overseas clinical trial data
  - The generation process of overseas clinical trial data should comply with relevant requirements of ICH's GCP
  - Applicants should ensure the design of clinical trials are scientific, the quality management systems of clinical trials comply with the requirements, and that clinical data statistical analysis is accurate and integrated
  - For applicants that undertake drug research and development synchronously in China and abroad (ex-China), for which the clinical trials are to be conducted in China, in order to ensure the scientific nature and validity of clinical trial designs and data statistical analysis, applicants/sponsors may communicate with CDE before conducting the pivotal clinical trials so as to ensure that the trial designs are consistent with the basic technical requirements for drug registration in China |
| Adjusting the Approval Process for Drug Clinical Trial Evaluation (Circular 50) | Circular 50 was released by NMPA on 27 July 2018. The intent of the circular’s release was to encourage innovation, speed up the creation of new drugs, meet the needs of public drug use, and implement the responsibility of the applicant’s research and development, according to the General Office of the CPC Central Committee and the General Office of the State Council “Opinions on Deepening the Reform of the Examination and Approval System and Encouraging the Innovation of Pharmaceutical Medical Devices,” related to the review and approval of drug clinical trials.
  - For drug clinical trial applications in China, if, within 60 days from the date of application acceptance and payment, the applicant has not received a refusal or questions from CDE, the drug clinical trial may be carried out in accordance with the submitted clinical trial protocol |
| MAH pilot project extended one year                                   | On 26 October 2018, in order to better summarize the pilot experience of the MAH pilot project, to lay down a good foundation for reform and improvement of the drug management system, and to pave the way for the revision of the Drug Administration Law of the People’s Republic of China, The Sixth Session of the Standing Committee of the 13th National People’s Congress (NPC) decided that the three-year period for the MAH pilot project should be extended by one year.
  - This pilot project authorized the State Council to launch the MAH system in some places at the 17th meeting of the Standing Committee of the 12th NPC on 4 November 2015
  - This decision came into force on 5 November 2018 |
Table C: Reforms 2018 (continued)

<table>
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| Accelerated approval          | On 30 October 2018, the NMPA official website issued the “Notice on the Release of the First Batch of Clinically Urgently Needed New Drugs List.”  
In order to implement the spirit of the meeting of the State Council and speed up the urgent need for new overseas drugs to enter China, NMPA and NHC formulated the “Clinical Urgent Need for Overseas Drug Evaluation and Approval Work Procedures”:  
• There are eight new overseas drugs that have been approved recently, and the list of the other 40 new overseas drugs has now been announced in accordance with the procedures
  
**Review and Approval Procedures for Overseas New Drugs pdf**  
Drugs in the urgently needed new overseas drug list may be submitted in accordance with the “Clinical Urgent Need for Overseas New Drug Evaluation and Approval Work Procedures,” and the NDA shall be directly submitted.  
• CDE shall establish a special channel to expedite review  
• If the NDA has not yet been submitted, the applicant can contact CDE at any time for consultation meeting and submit the NDA as soon as possible |
| Independent Vaccine Administration Law | On 11 November 2018, NMPA published the draft version of Vaccine Administration Law for public comments.  
Shaken by the Changsheng Bio-technology Co in Changchun vaccine scandal Changsheng Bio-technology Co, the vaccine manufacturer, which is based in Jilin province, was found to have committed serious law violations by China’s drug authorities in July and August in connection with the production of a rabies vaccine. The violations included fabricating production records and using expired ingredients), the Chinese authority will legislate via an independent Vaccine Administration Law in parallel with pharmaceutical products. The new Vaccine Administration Law aims to impose “the strictest” regulations on vaccines to ensure the safety and quality of these products. The new law intends to improve China’s vaccine management system and eliminate regulatory loopholes exposed by the scandal.  
Under the released draft, health and drug authorities will supervise the entire production chain of vaccines. Drug authorities should also be more thorough in inspecting vaccine production sites. Manufacturers must digitally record data related to production and inspection of vaccines and must also certify the authenticity, integrity and traceability of the data, according to the draft document. Approval procedures and inspections must cover every batch of vaccines before they enter the market. Authorized institutes must inspect and approve vaccines and report to China’s top drug authority and provincial-level drug authorities if there are any major safety or quality risks found, so that they can be dealt with immediately.  
Serious violations of the law, such as producing fake or substandard vaccines, will receive harsh penalties. |
### Table C: Reforms 2018 (continued)

<table>
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<tr>
<th>Reform</th>
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<tr>
<td>CDE website</td>
<td>In December 2018, CDE website added new functions on IND to allow the public access to the IND application (including progress, supplement notice, and download of IND permission). This was previously accessible by applicant only. So far, eight IND permissions were made public on the CDE website, signifying the formal establishment of the system in China.</td>
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### Reform Impacts: 2019

### Table D: Reforms 2019

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<th>Reform</th>
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<td>Medical device site qualification notification(^{19})</td>
<td>From 1 January 2019, all sites participating in a medical device clinical trial shall complete their medical device site qualification notification, which was according to “Medical Device Clinical Study Institution Notification Regulation,” [CFDA Notice 2017 No. 145], effective from 1 January 2018; transition period until 31 December 2018. The status of medical device site qualification notification is now available on the old NMPA website via the link below (data migration ongoing).<a href="http://218.240.145.213:9000/CTMDS/apps/pub/public.jsp#">http://218.240.145.213:9000/CTMDS/apps/pub/public.jsp#</a></td>
</tr>
<tr>
<td>MAH ADR direct reporting system online</td>
<td>This system is associated with the NMPA reform of adverse drug reaction (ADR) reporting which emphasises that MAH is the main responsible body of pharmaceuticals is now online.</td>
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<tr>
<td>Oncology and rare disease drugs(^{20})</td>
<td>China will further shorten the time required for the registration and approval of new oncology drugs and cut prices, a State Council executive meeting chaired by Premier Li Keqiang decided on 11 February 2019. Experts will select overseas new drugs to meet urgent clinical needs, while import policies will be improved for faster launch of the drugs in China. China will step up efforts to ensure more early diagnosis and treatment of cancer, and offer preferential value added tax (VAT) policies for drugs for treatment of rare diseases. Starting on 1 March 2019 for the first group of drugs, which includes 21 drugs for treatment of rare disease, VAT will be 3% to align with oncology drugs.</td>
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<tr>
<td>Collaboration network for rare disease diagnosis and treatment⁴¹</td>
<td>China will establish a national collaborative network of hospitals for rare disease diagnosis and treatment to promote the early detection and effective treatment of such diseases, according to a decision by NHC.&lt;br&gt;&lt;br&gt;Comprised of 324 hospitals selected for their capacity and experience in treating patients with rare diseases, the network will facilitate the timely transfer of difficult and complicated cases between hospitals and the allocation of quality medical resources for them.&lt;br&gt;&lt;br&gt;Meanwhile, hospitals in the network are urged to further train medical workers on rare disease knowledge and clinical skills, focusing on improving their abilities to identify, diagnose and treat such cases.&lt;br&gt;&lt;br&gt;China will establish a system for rare disease patients to be registered.</td>
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<td>2018 CDE performance review meeting⁴²</td>
<td>In their performance review meeting, CDE looked at key achievements in 2018:&lt;br&gt;• Enforcement of process reform&lt;br&gt;• Implementation and acceleration of the approval of urgently needed overseas new drugs¹⁶&lt;br&gt;• Reducing approval process time for drug clinical trial evaluation¹⁴&lt;br&gt;• Excipient/active ingredient/package material bundling review&lt;br&gt;• China marketed drug catalogue (Orange Book)&lt;br&gt;• GQCE⁹ and ICH&lt;br&gt;• Total of 7,336 applications submitted to CDE, 9,796 applications with evaluation completed, and backlog reduced to 3,440 applications (a reduction of 14 percent compared to 2017)&lt;br&gt;&lt;br&gt;In 2018, a batch of new and effective drugs for public health prevention and control, oncology, rare diseases and other urgently needed drugs completed the technical review and approval process, which provided motivation for innovation in research in China.</td>
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<td>4+7 drug volume purchasing⁴³</td>
<td>The purpose of 4+7 volume-based purchasing policy is to cut the drug price, increase market access, and support reform of the healthcare system.&lt;br&gt;&lt;br&gt;Although the National Health Insurance Bureau has successively published explanations for the policy, this policy still shook the pharmaceutical industry. For mature products entering into the policy scope, the price pressure is very high and industry is concerned about whether the purchase price reduction and quantity are complementary. Innovation is undoubtedly the direction that is key in the future.</td>
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Table D: Reforms 2019 (continued)

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| 2019 report on the work of the government\(^24\) | 2018 key achievements in healthcare included:  
- Continuation of coordinated medical service, medical insurance, and pharmaceutical reforms  
- Made steady progress in developing the tiered diagnosis and treatment model  
- Raised the level of government subsidies for rural and nonworking urban residents' basic medical insurance and the reimbursement rate of their serious illness insurance  
- The reform for evaluation and approval of new medicines was stepped up; the prices of 17 oncology drugs were slashed and these drugs were included in the national medical insurance catalogue  
- Strengthened oversight over food and drug safety, and investigated and took stern action in defective vaccines cases  

Tasks in 2019 included:  
- Strengthen research and development and the application of big data and artificial intelligence technologies; foster clusters of emerging industries like biomedicine  
- Ensure access to basic medical and health services; continue to increase basic medical insurance and serious disease insurance protection for rural and nonworking urban residents; lower and unify the deductible line for serious disease insurance, raise the reimbursement rate, and further reduce the burden of medical care for people with serious diseases and people living in poverty  
- Strengthen the prevention and treatment of serious diseases; take action in cancer prevention and treatment, and promote preventive screening, early diagnosis and treatment, and breakthroughs in cancer research  
- Improve prevention and treatment of common chronic illnesses. Outpatient medicines for treating high blood pressure, diabetes, etc., will be made reimbursable under the medical insurance scheme  
- Implement and improve the policy on interprovincial on-the-spot settlement of medical bills through basic medical insurance accounts; enable patients to use their medical insurance cards for medical treatment in any designated hospital and settle their bills straight away regardless of the locality  
- Continue the reform of public hospitals, and encourage the development of privately run hospitals  
- Establish a system for remote medical care services, enhance the training of community medical workers, and improve services provided both under the tiered diagnosis-and-treatment model and by contracted family doctors  
- Prevention will continue to be a priority  
- Maternal and child healthcare services will be improved  
- Support the preservation, innovation, and development of traditional Chinese medicine  
- Strengthen the entire process of regulation of drugs and vaccines from production to use |
Table D: Reforms 2019 (continued)

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| eCTD implementation progress and plan | On 8 March 2019, CDE presented the electronic common technical document (eCTD) progress and plan in the annual meeting of the China Association of Pharmaceutical Equipment.  
• The China specification and technical requirements are published for public comments in March 2019  
• China eCTD pilot implementation date will be May 2019; no formal implementation timeline available yet  
• In the early phase, submission of dossier will use CD plus hardcopy, and then transfer to gateway submission gradually  
• CDE suggested that the industry should be well prepared for eCTD  
• For cost efficiency, small- and medium-sized companies may consider outsourcing (to CRO) |
| Medical Device Animal Study Technical Review Guideline Part I: Decision Principles | NMPA issued “Medical Device Animal Study Technical Review Guideline Part I: Decision Principles” on April 19. The guideline provided the principles considerations on using live animal for medical devices development, decision tree and listed 12 devices as examples to discuss if study in live animals is needed:  
1. Porous coated bioprosthetic hip prosthesis  
2. Electrocardiography machine  
3. Cross-linked sodium hyaluronate gel for injection  
4. Absorbable hernia patch  
5. External defibrillation products  
6. Ultrasound soft tissue cutting hemostasis system  
7. Implantable pacemaker  
8. Drug eluting stent  
9. Degradable metal screws for internal fixation  
10. Stapler  
11. Anastomat  
12. Absorbable surgical anti-adhesion product |
| Medical device online registration system starts in June 2019 | CMDE (Center for Medical Device Evaluation, NMPA) announced that medical device online registration system (eRPS) is implemented in June 2019. This system allows local Category 3, import Category 2 & 3 medical device registration and Category 3 high risk medical device clinical trial applications. E-submission is optional and paper dossier under current requirement are still allowed before October 31. From November 1, submission dossier including paper and e-dossier should follow the Table of Contents by International Medical Device Regulators Forum (IMDRF).  
This is the gateway for the online submission. http://erps.cmde.org.cn/ |
### Table D: Reforms 2019 (continued)

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<td>Approval procedure of medical device clinical trial permit application changed to implied approval&lt;sup&gt;27&lt;/sup&gt;</td>
<td>On 1 April 2019, NMPA issued the Adjustment of Medical Device Clinical Trial Approval Procedure. Since the date, for clinical trial permit application, if no feedback from NMPA within 60 working days, sponsor can directly start the clinical trial. NMPA will no longer issue the trial approval letter. Similar to drug, applicant can download and print the trial approval letter from NMPA website. If necessary, pre-IND meeting can be required by sponsor. Other requirements of medical device clinical trial, continuous follow the Registration Regulation of Medical Device.</td>
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<td>Second batch of clinical urgently needs overseas new drugs&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Following the 1st batch released in October 2018, CDE released the 2nd batch of drug products of urgent medical needs in China on 29 May, in which 26 products are included. If there is no ethnic difference, local clinical trial data can be waived for NDA/BLA. The new drugs added include orphan drugs, pediatric drugs, also include treatments for life-threatening diseases for which there is either currently no approved product, or for which the new drug offers a substantial clinical advantage over existing approved therapies. The draft list was published for public comments in March.</td>
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<td>NMPA advancing regulatory science initiatives in drug and medical device in China&lt;sup&gt;29&lt;/sup&gt;</td>
<td>In April 2019, NMPA initiated the strategic plan of China Regulatory Science project and identified nine priority areas in first batch. The areas include cell and gene therapy products, nanomedicine, drug-device combination products, post-market drug safety vigilance and evaluation, AI devices, new material in medical devices, real world data for medical device, and safety assessment of Chinese traditional medicine and cosmetics. Three key objectives for the project are specified: establish 3-5 bases for regulatory science; initiate key regulatory science projects; introduce series drug evaluation and supervision policies/tools/standards/methods.</td>
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| **State Council releases legislative work plan for 2019**<sup>30</sup> | State Council announced the China 2019 legislative work plan in May 2019. Four healthcare related legislation are involved:  
1. Regulation of safety in Biotech development (lead by Ministry of Science and Technology)  
2. Regulation of clinical practice management on new technology of biomedical (lead By NHC)  
3. Human Genetic Resource Administration of China (lead by Ministry of Science and Technology)  
4. Revision of Regulation of medical device management (by NMPA) |
| **CDE solicited public comments on Key Considerations in Using Real World Evidence to Support Drug Development**<sup>31</sup> | Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions. In China, CDE has already begun to utilize RWE in the review practices. This guideline will facilitate industry and CDE to clarify the scope of RWE, explore the principle of the RWE evaluation, and provide a feasible guidance to use of the RWE. |
| **NHC solicited public comments on third batch of encouraging drug list for pediatric**<sup>32</sup> | The third batch of encouraging drug list for pediatric selection is led by NHC and national pediatric expert committees. The screening principles are: not registered in China, urgently unmet medical needs, evidence-based, expert opinion. |
## Reform/Detail/Opportunity

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<td>State Council issued the human genetic resources management regulations[^33]</td>
<td>National regulations on the management of human genetic resources recently released by the State Council, which will go into effect on July 1. The regulations apply to the collection, preservation and using of a range of genetic materials containing human genomes and genes (organs, tissues and cells) and impose requirements on human genetic resource information (data derived from the genetic resource materials). It is issued to regulate and encourage reasonable employing of human genetic resources in scientific researches, developing biological medicine (drugs or medical devices) and improving diagnosis and treatments. According to the regulations, foreign organizations and individuals, as well as organizations directly controlled by them, are not allowed to collect or preserve China's human genetic resources, nor is providing such resources abroad. Collecting, preserving, utilizing, and providing human genetic resources abroad should be in accordance with ethics principles, submit to corresponding ethics investigations, and meet the technical standards formulated by scientific administrative departments of the State Council, with no violations on the country's public health, national security, and public interests. Sales of human genetic resources are prohibited, said the regulations. It is mentioned in the regulation that “In order to obtain the market approval of relevant drugs and medical devices in China, international cooperative clinical trials conducted in clinical institutions using human genetic resources of China, which do not involve the exit of human genetic resources materials, do not need approval” During the period before effective date, applications accepted before 5 pm 28 June 2019 will follow the “old” procedure. Applications accepted after this time point will follow the procedure in the new regulation.</td>
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<td>NMPA published the Medical Device registration 2018 annual review[^34]</td>
<td>In June, 2019, Jiao Hong, Director of the NMPA, attended the first BBS conference on global health in Boao Asia BBS. Jiao Hong said that China, as an important part of the global pharmaceutical supply chain, is providing a large number of high-quality pharmaceutical products to the world. NMPA always gives top priority to public health protection, adheres to the bottom line of drug safety, promotes innovative development, improves regulatory capacity, and deepens international cooperation, so as to make every effort for drug safety and effectiveness and contribute to global health. During the meeting, Jiao Hong met with who Deputy Director-general Dr. Suzanne Jacobs and GAVI CEO Dr. Seth Berkley respectively, and had in-depth discussions on topics such as vaccine regulatory system, drug and vaccine pre-certification, and innovative vaccine development.</td>
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[^33]: CHINA REFORM OF THE REGULATORY ENVIRONMENT
[^34]: CHINA REFORM OF THE REGULATORY ENVIRONMENT
Conclusions

The 2016-2019 reforms represent major changes for China’s regulatory environment and are expected to better align the country with global regulatory norms by:

- Reducing the IND (clinical trial) and NDA review timelines
- Strengthening the standards for generic drugs
- Reforming clinical trial data quality requirements
- Introducing a priority review process for innovative drugs
- Accelerating the registration speed for unmet medical needs

NMPA is clearly encouraging foreign sponsors and applicants to undertake global studies in China and recommends that local clinical sites are part of global studies to help ensure clinical trial data meet the requirements needed for China and for global registration. The clinical trial reforms announced by NMPA will hopefully overcome some of the reluctance of foreign sponsors to include China in global programs, as the IND review timeline of 60 days mirrors that seen outside of China.

It is anticipated that the new requirements for generic drug quality and efficacy evaluation and self-inspection of clinical data will upgrade generic drug standards, clinical trial quality and clinical site GCP compliance. It is acknowledged that these new standards may also present some initial challenges for generic pharmaceutical companies; however, CROs should be able to advise, fill any knowledge gaps and conduct required BE studies. This evolution is likely to provide a boost for China’s CRO industry, but it is likely that local CROs will face major hurdles as they attempt to enhance their own quality processes in order to meet NMPA’s stricter requirements. Sponsors will be motivated to use reliable CROs with established standards to manage their trials and generate reliable data to meet requirements and support approvals.

The reforms will undoubtedly benefit new drug innovators planning to conduct meaningful, scientific trials. This should ensure that trial site resources are used more effectively on good quality research, which will have a long-term, positive and profound impact on the Chinese pharmaceutical industry. 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.

More reforms can be anticipated, and indeed the Chinese government has already laid out some of the plans for 2019; therefore, it is essential that local Chinese regulatory expertise is available to closely monitor these changes and ensure accurate and timely communication to all relevant stakeholders. In addition, a robust Chinese regulatory strategy consultation or assessment will need to be prepared and agreed on much earlier than before so that Chinese activities can be effectively integrated into the global program from the start.
References

11. http://www.gov.cn/xinwen/2017-10/08/content_5230105.htm
33. http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm
About Syneos Health

Syneos Health® (Nasdaq:SYNH) is the only fully integrated biopharmaceutical solutions organization. The Company, including a Contract Research Organization (CRO) and Contract Commercial Organization (CCO), is purpose-built to accelerate customer performance to address modern market realities. Learn more about how we are shortening the distance from lab to life® at syneoshealth.com.