ROPES & GRAY

Every Single Step Counts for a Journey of a Thousand Miles

Partnering for an Innovation-Conducive MedTech Regulatory System in China

By **Katherine Wang** and **Xiaoyi Liu**

The authors would like to thank **Florian Then** and **Kevin Wu** of McKinsey & Co. for their valuable insights and inputs to this work.

Key Regulatory Developments in 2016

Since the inception of the State Council's *Regulations on the Supervision and Administration of Medical Devices* (Order No. 650), China's regulatory landscape for medical devices continued to unfold in 2016 and 2017. The CFDA issued more technical review guidelines to clarify its expectations for the contents of regulatory submissions. The regulator also issued and updated more technical standards across a wide range of product categories and technical areas, urging the industry to upgrade device safety and effectiveness. Last but not least, in the past two years the CFDA issued several new regulations that have a significant impact on the MedTech industry:

- *Good Clinical Practices for Medical Devices (GCP)*, which introduces more scientific and rigorous clinical trial requirements;
- *Clinical Trial Exemption List of a second batch of medical devices (including 92 Class III devices and 267 Class II devices),* which exempts more devices from clinical trials;
- *Rules on Generic Names of Medical Devices,* which sets forth uniform naming rules for medical devices;
- *Procedures for Priority Review of Medical Devices,* which creates a new expedited approval pathway for devices with apparent clinical values and addressing urgent clinical needs, or those receiving research funding from the national major scientific/R&D programs;
- *Medical Device Classification Catalogue (draft for public comments),* which updates the classification methodology for devices based on their risk profiles;
- *Medical Device Good Review Practices*, which streamlines and standardizes the review and consultation processes at the Center for Medical Device Evaluation; and
- *Provisional Measures on Communications and Exchanges during Medical Device Reviews,* which formally frames the consultation mechanism between device applicants and reviewers.

Along with legislative efforts, the CFDA has also significantly stepped up its law enforcement efforts in the "Post-Order No. 650 Era." For example, the CFDA has increased the frequency of regular quality inspections, aiming to crack down on products that are not consistent with the mandatory technical standards or their registered technical specifications. The CFDA has also enhanced its supervision over companies' product development, manufacturing and distribution activities to ensure compliance with China's GCP, GMP and GSP standards.

The CFDA's active shaping of the regulatory environment poses new challenges and opportunities for regulatory affairs ("RA") professionals. According to the survey result conducted among 18 RA leaders from leading medical device companies that participated in the 2017 China MedTech Regulatory Affairs Roundtable, the following regulatory changes or trends in the past 1-2 years are considered most material:

Using clinical evaluation report to waive local clinical studies

For Class II and III devices, the CFDA regulations have made local clinical trials mandatory except if the underlying technology is proven to be safe and effective.[1] The CFDA in principle admits foreign clinical study data, but holds a very firm standing on the topic of ethnicity difference. It is usually not possible to substitute clinical data on Chinese patients with foreign clinical studies.

Clinical trial exemption is possible if the product is listed on the trial exemption list that the CFDA updated from time to time. In 2014 and 2016, the CFDA released two exemption lists covering in total 171 Class III devices and 755 Class II devices, all of which are mature product categories. Clinical Evaluation Report

("CER") is another mechanism for clinical trial waiver.[2] Similar to the USFDA's 510(k) pathway, CER allows manufacturers of new devices that are substantially equivalent to previously approved predicate devices to demonstrate safety and effectiveness by a comprehensive comparison of technical features and clinical performance.

Clinical trial audits for GCP compliance

On March 23, 2016, the CFDA and NHFPC jointly promulgated the new GCP governing medical device clinical studies, the first revision in 12 years to replace the original *Provisions on Medical Device Clinical Trials* issued in 2004. The new GCP generally strengthened the responsibilities of sponsors, detailed the requirements for seeking informed consent and enhanced protection of subject's rights. It also provided more stringent requirements for record-filing with local FDAs, management of study devices, and documentation/archiving.

To urge compliance with the enhanced GCP standards, the CFDA initiated several rounds of GCP audits since July 2016. Upon conclusion of the CFDA's 2016 GCP audits, 8 device applications were found with data authenticity issues and were rejected by the CFDA, while another 122 applicants voluntarily withdrew their 263 applications with potential data integrity issues.

More technical standards issued and updated

The CFDA issues technical standards from time to time to upgrade the baseline for device safety and effectiveness. Products seeking marketing authorizations in China must meet the mandatory standards, but there are cases where a product's unique technical features do not fit well into the mandatory standards. Recommended standards are optional, but sometimes reviewers at the Center of Medical Device Evaluation (CMDE) can require applicants to include certain recommended standards in a product's technical requirements (PTR). Products fail to comply with the mandatory technical standards or the CFDA-approved PTR are deemed defective, and must be recalled by their manufacturers.

China's technical standards are not always harmonized with the current international standards. While the CFDA may consult industry representatives when setting the standards, Chinese MedTech companies are more likely to be involved and more easily contribute to this process than their foreign peers. This is largely because changes to the standards, if proposed by foreign companies, will often require validation to be performed outside China. As a result, China's technical standards can reflect the latest technology deployed by local MedTech industry, but it may not be timely synchronized with the latest trends in research and development worldwide.

Intensified post-market enforcement and quality inspections

Both the CFDA and its local counterparts periodically conduct quality inspections. Local FDAs frequently compare information in the product registration certificates with the actual labels. They also send randomly collected samples to type testing centers for verification tests against PTRs or mandatory standards. Companies will be penalized when their products bear incorrect labeling information, or are found to deviate from the registered PTR or the mandatory standards. The administrative penalties can range from 10 to 20 times of the sales of affected products.

MedTech companies have had issues with inconsistent interpretation of compliance requirements by local enforcement authorities. A growing number of local governments have consolidated administrations of industry and commerce, FDAs and administrations of quality inspections into a single Market Supervision Administration ("MSA"). The majority of MSA officers enforcing Order No. 650 is not from the FDAs and does not possess the technical knowledge to ascertain if products on the market comply or deviate from the registered labeling information or standards.

[1] Before initiating clinical studies, companies need to meet a number of prerequisites. These prerequisites range from Clinical Trial Authorizations for certain high risk devices, a satisfactory type testing report, the EC approvals, and the completion of a record filing with the relevant local FDA.

[2] The CFDA's *Technical Guidelines governing Medical Device Clinical Evaluation,* effective as of May 19, 2015.

Increasing efforts in GMP and GSP inspections

MedTech companies have perceived increased GMP and GSP inspections in recent years, which are conducted from time to time by the CFDA or its local counterparts. Both import and domestic device manufacturers must meet China's GMP standards throughout their product development and manufacturing cycles. For imported products, the CFDA has since 2016 organized several rounds of post-approval GMP inspections of selected foreign facilities and issued its notices of observations and deficiencies, and may expand the scope and frequency of overseas inspections in the future. For device distributors, in June 2016 the CFDA required all Class II and III device distributors to conduct self-audits of their GSP compliance since June 1, 2014, and to identify and report any material issues of non-compliance. Those who refused to disclose material issues of non-compliance can receive severe penalties and can face revocation of the device distribution license.

Implications for MedTech Companies

The regulatory regime in the Post-Order No. 650 era has two main implications for MedTech companies: first, long registration timelines (even for innovative devices) remain unresolved, and second, there is considerable unpredictability associated with post-approval quality supervision and enforcement.

Long product approval timelines

The promulgation of Order No. 650 did not significantly accelerate the new product approval timelines. Our survey of leading MedTech companies suggested that the long timeline for new product approvals can be attributed to the complicated requirements for local clinical study, the lack of pre-submission consultation opportunities with the CFDA, and the shortage of qualified type testing centers.

The CFDA introduced several regulatory requirements for clinical trials in the Post-Order No. 650 era. The complexities associated with clinical studies can discourage both local and foreign innovative MedTech companies from launching new products in China. Our roundtable participants noted the following causes for the long approval timelines.

1. The clinical trial exemption lists have not been regularly updated, and the listing criteria remain puzzling. Companies often find it challenging to timely and effectively input on the CFDA's catalogue updating process. Leveraging CERs to apply for clinical trial waiver has been challenging. The CFDA does not proactively reference its review dockets concerning predicate devices to ascertain the question of substantial equivalence. Instead, the CFDA expects companies to gain authorization and access to competitors' predicate device data. While the CMDE reviewers could impose different requirements for the forms and contents of the authorization letter, it is practically very hard to present convincing evidence of equivalence if the predicate device is developed by another company. Besides, foreign device manufacturers may not be able to substitute clinical data on Chinese patients with foreign clinical studies, because the CFDA holds a high bar for proving the absence of ethnicity differences. As a result, CER is only successful in very limited scenarios, such as the localizing an established, approved imported device in China, or registering incrementally upgraded versions of an approved device of the same applicant. Although well intentioned, it is considerably less efficient than comparable processes in mature markets such as the US 510(k) process, which predictably leads to an approval in just over a year for eligible products. Last but not least, while our roundtable participants applauded the CFDA's determination to sanction data falsification, they also noted that hospitals and physicians become reluctant to participate in clinical studies. The shortage of qualified sites and investigators may make it harder and more costly to conduct clinical studies in China.

2. Another concern is insufficient pre-submission consultation opportunities with regulators. Except for fast track applicants, companies can only engage the reviewers on substantive questions after receiving deficiency notices from the CMDE regarding pending applications, but it is generally not possible to obtain formal guidance regarding applicable standards or study requirements prior to the submissions are made.
3. The government recently canceled type testing fees charged by government accredited testing labs. While companies previously may choose to pay extra fees for expediting their type testing submissions, they are not able to do so anymore. There are worries that without permitting private labs to offer type testing services, companies may experience further slow down in the handling of type testing by governmental labs.

Considerable unpredictability associated with post-approval quality supervision and enforcement

The CFDA has shifted its regulatory emphasis from pre-market supervision to post-market enforcement. FDAs at the national, provincial and district levels have been actively enforcing the GCP, GMP, and GSP requirements, as well as various compliance requirements in Order No. 650. MedTech companies welcome the shift in the regulatory paradigm, but have been frustrated with the unpredictability associated with post-approval quality supervision and enforcement across different provinces/counties. The unpredictability is partially attributed to differences in the underlying technical and quality standards, and also attributable to differences in local FDAs' enforcement standards.

1. One major cause for post-approval enforcement risks is the product's failure to comply with China's mandatory technical standards or CFDA-approved PTRs. The technical standards for MedTech products in China carry their unique characteristics and are not always aligned with the latest international standards. This may present issues for MedTech companies trying to sell products around the world—both MNCs playing in China and local Chinese companies seeking global expansion. Many MedTech companies historically develop products centrally for global markets. These products might have certain inherent discrepancies with China's mandatory standards. Although companies can try to incorporate such mandatory standards into the PTRs in order to satisfy the regulators' requirements, they may not be able to completely follow the prescribed testing methods and parameters in the actual manufacturing process. Also, China's mandatory standards could be too rigid and overreaching. They do not allow necessary product-specific differences and can restrict the application of scientifically sound technologies. Conversely, local Chinese MedTech champions who are setting out to expand into international markets will face just another hurdle as their product development and quality processes will be tailored to Chinese requirements which may not match requirements of other major markets.

2. The new device GMP also imposes pressure on both local and multinational device companies. After the CFDA rolled out new device GMPs that came into effect in March 2015, domestic manufacturers perceived an increase in the frequency and stringency of GMP inspections, which can be conducted from time to time by the CFDA, as well as by the municipal and provincial FDAs. The CFDA also has committed more personnel and resources to overseas inspections of foreign manufacturers that market devices in China. While the principles of the device GMP are compatible with ISO 13485, the actual inspection

approach and priorities of the CFDA can differ from international notified third parties. MedTech companies with global business will need to carefully analyze the differences and develop a quality management system that is effective yet adaptive in order to cope with different regulatory bodies' demands.

3. The local FDAs' discretion in interpreting regulations and characterizing misconduct significantly affects and varies the scale of the penalties. According to our Roundtable survey, almost half of RA leaders worry that the device regulations may still be implemented in a fragmented manner by local FDAs three years after the promulgation of Order No. 650. Meanwhile, in some regions, local FDAs have merged with other agencies such as the AIC (Administration of Industry and Commerce) and AQSIQ (Administration of Quality Supervision, Inspection and Quarantine). The enforcement of device regulations can be in the hands of officers previously with the AIC or AQSIQ, and their lack of understanding about the device companies' business practices may affect the interpretation of device regulations.

Product Launch Challenges Call for Further Regulatory Reforms

It goes without saying that the "pain points" described above burden local and MNC MedTech companies with additional uncertainties and cost. Perhaps most importantly, they lead to lost opportunities from delayed launches—or possibly even deferred launches—of innovative products.

This raises the question as to whether regulatory hurdles might actually impact the availability of innovative medical technology to China's patients and care givers. A look at past product launches abroad and in China suggest that that there is indeed a "launch gap": For example, of 150 PMA first approved medical products between 2010 and 2014 in the U.S., only 47% are currently available in China, and less than 5% are in regulatory approval process. In other words, 50% of the products are presently not available for patient care in China, and most of them may never be launched.

To be sure, product launch decisions are multi-factorial and regulation can certainly not take sole blame for forgone launches—however, it is clear that lengthy, complex regulatory approval processes are one important deterrent for companies to launch products in international markets.

Partnering for an Innovation-Conducive MedTech Regulatory System in China

What can the industry do to get more involved in shaping a regulatory system that fits the China market? Given the fast development of China's regulatory landscape, most companies have been busy just coping with the changes—starting from interpreting regulatory guidance to defining the space of possible solutions to devising and implementing responses.

A more effective way for both the regulators and the companies would be to shape policy in a collaborative way balancing the interests of patients, the healthcare system and the MedTech industry. Despite this obvious truth, it has been difficult for China's MedTech industry to find a platform and speak with "one voice" on matters important to the industry, in a way perceived as balanced and impartial, avoiding suspicion of being "self-serving." For example, divergent agendas of local and MNC companies (perceived or real) have so far been in the way of establishing an industry association that could credibly represent the interests of local and MNC MedTech companies alike.

Positive impulse is coming from the government itself, indicating that China's regulatory authorities are aware of the imperfections of the system, and working on improving it. In the form of a set policy drafts for public comment in May 2017 (circulars 52-55), the CFDA is suggesting solutions for several of the issues described

above, sometimes through bold suggested steps. Highlights of these suggested regulatory changes include:

1. Expedited reviews and approvals for new therapies that are life-saving, targeting rare diseases, or otherwise addressing a critical unmet need. The key here is that conditional approvals can be granted even based on early- or mid-stage clinical trial data if the data suggest efficacy and clinical value
2. Further professionalization of the review system, with clearly assigned reviewers for each application, a cadence of consultation meetings at key milestones of the clinical trial process, and cross-disciplinary teams which should be able to make decisions faster based on their combined expertise
3. Several measures to address bottle necks in availability of clinical trial infrastructure – most notably, a proposal to replace the current certification system to qualify clinical study sites with a more practical audit of actual ongoing studies. In addition, incentives for medical facilities and physicians to participate in clinical trials are part of the plan. Along similar lines, third parties are to be involved for technical reviews to provide adequate capacity, and an electronic document filing system should streamline application processes
4. Obligation for the CFDA to respond to clinical trial applications within 60 days with a rejection or deficiency notice. In the absence of such notice, the application would be automatically approved
5. Permission for foreign companies to use foreign clinical trial data to support registration in China (although the requirement to prove that no ethnicity difference affects the product's safety and efficacy will continue to be with the manufacturer according to the new draft).

These and some other proposed policy changes demonstrate a thoughtful approach to the issues of regulatory approval in China. At the same time, the circulars are also proposing tighter adverse event reporting rules, rigorous post-market audits and inspections, and further regulation of sales representatives' promotional activities.

With much of the regulatory landscape once again "on the move" and actively put up for discussion and input by an increasingly experienced and sophisticated regulatory body, now is a good time for the industry to engage and jointly shape the future of MedTech regulation in China. It will be up to the Regulatory Affairs leaders and business leaders to seek this opportunity and demonstrate their added value in building a regulatory framework that is worthy of China as one of the world's largest and most dynamic MedTech markets, while taking into account the unique needs and constraints of China's healthcare system with its still unresolved challenges of broad access to quality healthcare.

As a first and perhaps most important step, the MedTech industry in China should find a platform to develop a true industry-wide perspective and speak with one voice across the boundaries of local Chinese and foreign MedTech companies. While China's goal is to create a regulatory framework that fosters innovation, we recommend that such platform address the needs of both local and foreign innovation-minded MedTech companies. These companies often share a similar agenda: they focus on development of innovative devices and aspire to benefit patients in the global community. The CFDA's regulatory reform should respond to the desire of these innovation-focused MedTech companies and eventually make China a fertile land for cultivating world-class innovative devices.

Katherine Wang is a partner in Ropes & Gray's Shanghai office and leads the firm's China life sciences regulatory practice.

Xiaoyi Liu is an international associate in Ropes & Gray's Shanghai office and has frequently assisted multinational medical device companies with issues relating to regulatory approvals and market access.

HONG KONG | SHANGHAI | SEOUL | TOKYO
NEW YORK | WASHINGTON, D.C. | BOSTON | LONDON
CHICAGO | SAN FRANCISCO | SILICON VALLEY

ROPES & GRAY
ropesgray.com

© 2017 Ropes & Gray LLP. All rights reserved. Prior results do not guarantee a similar outcome. Communicating with Ropes & Gray LLP or a Ropes & Gray lawyer does not create a client-lawyer relationship. 17_0941_0713