CHINA'S MEDICAL DEVICE MARKET

Coping with Evolving Regulatory Challenges

Ask a senior manager of a MedTech company in China what keeps her or him awake at night and "regulatory changes" will invariably be among the first things mentioned. In fact, in McKinsey's 2016 survey of MedTech CEOs, regulation tops the list of critical issues MedTech leaders face.

Correlating to this high level of attention on the regulatory side, *Regulations on the Supervision and Administration of Medical Devices,* better known to many in the industry as State Council Order No. 650, stands out as a landmark policy update. Since its announcement in 2014, State Council Order No. 650 has brought a series of profound changes to the industry and impacted both local and multinational corporation (MNC) MedTech players in China.

On a functional level, regulatory affairs (RA) leaders have been most exposed to the new regulation, while at the same time taking an important role in shaping the implementation and interpretation of the new policies. As in previous years, the annual China RA roundtable (jointly hosted by Ropes & Gray and McKinsey & Company) provided a forum for RA heads of leading local and MNC MedTech companies and sparked insightful discussions at the latest one on regulatory changes and best practices in operating within the new regulatory paradigm.

This paper builds on the highly relevant discussions from the RA roundtable and provides an update of the major regulatory changes and their impact on the industry. We will discuss implications for the role and standing of the RA function in medical device companies, and how the RA function needs to evolve in anticipation of future trends.

Update on China's Regulatory Environment

Since the implementation of State Council Order No. 650, sweeping regulatory changes have affected China's medical device industry. In the past two years, the CFDA has issued dozens of guidelines for technical reviews and mandatory standards for medical devices, urging the industry to upgrade device safety and effectiveness. The CFDA also implemented a number of measures to streamline product approval and foster innovation. More recently, the CFDA issued *Good Clinical Practice for Medical Devices* (GCP), a new revision imposing higher compliance standards on the conduct of clinical trials by medical device companies.

Now more than a year into the implementation of the new regulation, four areas emerge as having particularly high impact on the industry and hence need to be understood thoroughly by MedTech organizations. These areas are:

- Comprehensive clinical trial requirements
- Streamlined product approvals
- Strengthened GMP audits, home and abroad
- Intensified post-market enforcement

Comprehensive clinical trial requirements

In August 2014, the CFDA released a *Catalogue of Class III Medical Devices Subject to Clinical Trial Authorizations* (CTA), significantly prolonging the clinical trial timeline of eight types of high-risk devices included in the catalogue. The statutory timeline for obtaining the CTA is 60-100 working days, while real-world experience by RA leaders suggests that it frequently takes six to nine months to obtain the CTA. In addition, prior to the CTA application, the sponsor must already collect the ethics committee approvals from all study sites, which can be a lengthy process. For an imported product, the sponsor must also obtain the marketing authorization issued by a foreign authority and include it in the CTA submission. The combination of these factors can substantially delay the initiation of clinical trials in China and prevent simultaneous cross-border development of innovative devices.

On the other end of the spectrum, clinical trials may now be omitted altogether in certain circumstances. Based on a CFDA guideline released in May 2015 (the *Technical Guideline Governing Medical Device Clinical Evaluation*), clinical trials can be waived on a case-by-case basis if the safety and effectiveness of a device can be demonstrated through nonclinical performance evaluations, or through clinical data from studies of a predicate device approved in China. However, one year after the launch of the clinical evaluation report (CER) mechanism, most of our roundtable delegates noted that, in practice, it remains challenging to obtain trial waivers through CER.

Streamlined product approvals

The CFDA now allows automatic renewal of licenses if there are no changes to the approved product. This mechanism is supposed to expedite license renewal. However, several of our roundtable delegates suggested that there is a lack of clear CFDA guidance as to what product changes would require reapplication or amendment submission. Some believe that an amendment submission is required for any changes to the listed items on the product license, while others believe an amendment submission is required only when the changes affect the safety and effectiveness of the device in question. Companies also differ as to whether they may proceed with amendment submissions in parallel to license renewals.

Another effort of the CFDA to streamline product approval was the introduction, on March 1, 2014, of a fast-track pathway for innovative medical devices. Under fast track, devices designated as innovative are given priority in the registration queue and applicants have more opportunities for consultation with examiners and experts. Fast-tracked products are also expected to be reviewed and approved relatively faster by the CFDA.

Strengthened GMP audits, home and abroad

The CFDA replaced the 2011 good manufacturing practice (GMP) regulations for medical devices with an updated version that came into effect in March 2015. All device manufacturers are expected to meet China's GMP standards throughout their product development and manufacturing cycles, whether they manufacture in China or overseas. With the new GMP, the CFDA committed more personnel and resources to quality system inspections.

Intensified post-market enforcement

With the rollout of the new regulations, the CFDA also significantly stepped up its post-market enforcement efforts. The CFDA launched a six-month enforcement campaign in 2014 targeting five common areas of noncompliance in the MedTech industry. In 2015, it launched another eight-month enforcement campaign targeting noncompliance in in-vitro diagnostics (IVDs). During these enforcement campaigns, the CFDA and local FDAs could both conduct periodic quality sampling. Companies might be penalized when their products are found to be not fully consistent with the registered technical specifications. This is of concern, as MedTech products often undergo incremental technical changes that may not be promptly submitted for approval in China. The inconsistencies between the actual product and specifications in CFDA registration information and labels can be targeted and challenged by local enforcement authorities. MedTech companies can face financial penalties in the range of 10 to 20 times the sales of products in question.

Given the high stakes in clinical trials, approval timelines, manufacturing quality standards and enforcement risks, medical device manufacturers must fully understand the current regulations and implementation rules. In addition, after the last round of systematic regulatory changes, most of our regulatory leaders believe that the regulations will keep evolving under the umbrella of State Council Order No. 650. A widespread concern is that the future regulatory landscape remains a moving target: According to our survey results, many RA leaders expect continuous regulatory changes in the next three to five years (55% of the respondents). In addition, most of them believe that the new device regulations will continue to be differently interpreted and implemented by individual provinces/cities (85%). On both counts, the answers indicating expected uncertainty have increased significantly versus a year ago, which indicates that implementation of the regulation has yet to enter a steady, predictable path.

Unaddressed Issues and Challenges

Among all the regulatory changes, clinical evaluation is consistently rated as the most relevant topic by all participating RA leaders. Interpreting and following the highly complex clinical trial authorization and the clinical trial exemption policies have presented the most challenges to their work. RA leaders also expressed their concerns about the costs and benefits associated with fast-track applications, the differences between the China GMP and ISO standards, and the unpredictability of post-market enforcement.

Clinical trial application is a lengthy and complex process

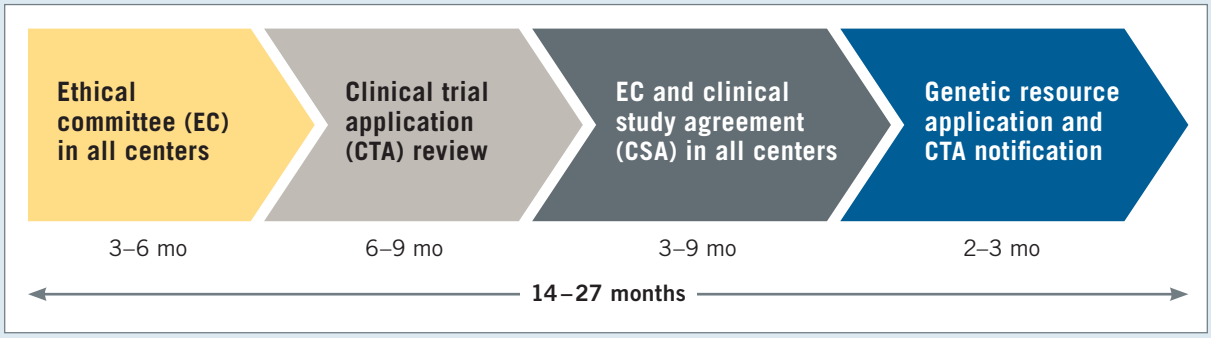
Clinical trial application in China is time-consuming: According to RA leaders surveyed, the average processing time (including queuing time) ranges from one to two and a half years, depending on the complexity of the clinical trial, with a median time of 21 months (*See Exhibit 1, top of page 4*).

Stringent and inflexible requirements, as well as the capacity constraint at CFDA/CMDE, are the root causes of the very long waiting time. For example, ethical committee approval is required for all centers participating in the trial. Obtaining such approval itself from all public hospitals can often be a tedious process.

Leveraging CERs to apply for waiver of clinical trial has been challenging. Companies can seldom gain authorization and access to competitors' predicate device data. Most known trial exemptions have arisen

Exhibit 1

Average Clinical Trial Authorization Process Steps and Timeline



in a few limited scenarios, such as the localized version of an established, approved imported device, or incrementally upgraded versions of an approved device of the same applicant. It is not clear whether the CFDA in practice recognizes cross-company data referencing during the clinical evaluation, as admitted under the 510(K) review regime of the U.S. FDA.

Despite the challenges, many companies will reserve CERs as the first option, but are prepared for local clinical studies. In the meantime, they also feel the need to push for more clarity and lobby for a more standardized process.

Balancing IP protection against the time to market

Given the long processing time, an increasing number of companies are now considering fast-track approval. According to the survey, 70% of participants are considering applying for fast-track status for future registrations (up from 40% last year).

On the other hand, many MNCs are concerned about intellectual property protection, and found it difficult to apply for the patent in China or initiate domestic operations. This is evident by the low proportion of approved applications to date from MNCs (among the 55 approved fast-track applications by April 2016, only four are from MNCs).

In practice, however, the benefits of fast track remain hard to grasp. Based on the feedback of our roundtable participants, the fast track cannot always reduce the uncertainties in CFDA's product review or deliver substantial time savings; for example, it may be still difficult to obtain detailed guidance from reviewers on the registration or study requirements of a designated device. Even if there is time saved in the CFDA's review phase, the time saving is also viewed as less significant, given that new devices need to undergo full-scale studies and a foreign marketing authorization is needed for initiating studies on an imported device in China.

Adapting manufacturing operations to China's latest GMP standards

After the CFDA rolled out new device GMPs, 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. For import manufacturers, the CFDA also announced the plan to roll out post-approval GMP audits of around 30 overseas device companies in 2016, a sharp increase from the two companies that received audits in 2015. The industry observed that the priorities and standards set out in the Chinese GMPs can differ from those under ISO 13485. Compliance with the requirements

of Chinese device GMPs is now a common area of concern for both Chinese and foreign players.

Post-market enforcement lacking consistency

Post-market compliance is increasingly challenging because local enforcement authorities can interpret statutory requirements inconsistently. The local FDAs' discretion in interpreting regulations and identifying and characterizing misconduct significantly affects and varies the scale of the penalties. RA leaders express concerns about a more aggressive enforcement style in some pilot regions where the local FDAs have merged with other agencies such as the AIC (Administration of Industry and Commerce). RA leaders also worry that the CFDA's regulatory requirements may sometimes conflict with the requirements of other supervising ministries such as AQSIQ (Administration of Quality Supervision, Inspection and Quarantine) and Customs, e.g., in terms of product labeling.

Coping with Evolving Regulatory Environment and Challenges

In a previous publication (available **here**) on the matter, following our 2015 China MedTech RA roundtable, we identified three priorities for achieving excellence in regulatory affairs:

- Developing seamless interactions between local regulatory affairs and the global team
- Becoming a valuable partner to regulatory bodies
- Building the capabilities of the regulatory team

We used the opportunity to take stock of these trends at this year's roundtable. Clearly, local-global interactions have been an area of focus, with over 70% of RA leaders reporting that more, or more structured, processes and interactions had been put in place over the past year. Over half of respondents also thought that the role and appreciation of the RA function within the local organization had increased and, accordingly, that the scope and focus of the RA team had evolved. However, only 30% had made structural changes to their organization (such as integrating the clinical affairs function with the RA function), and team-size increase was the exception rather than the norm, with 18% reporting additional hiring at the China headquarters level, and only 6% at a regional/provincial level. This points to the fact that the quality of RA talent is much more important than the quantity, and high-caliber talent remains the true bottleneck for many organizations. Interestingly, over 90% of RA leaders think that the key to improving their organization's readiness is in training and capability building, while only 20% believe hiring more people will be helpful in that respect.

While internally focused improvements at RA organizations are pursued across the industry, the question remains as to whether the collaboration between companies and regulators is fully leveraged to build a better regulatory environment for China. Again, 50% of RA leaders respond that efforts to work with the government have been stepped up over the past year. At the same time, approaches by individual companies inherently face certain constraints, as government stakeholders are, and should be, sensitive to what could be seen as lobbying efforts by individual players.

For this reason, cross-industry initiatives could play an important role in engaging the government in a more meaningful way. In fact, 70% of RA leaders believe that a thoughtful cross-industry channel approach could be a game-changer in the way MedTech companies work with the government. Interestingly, there is also a clear concern that current industry associations may not prioritize reform of the regulatory system on their agendas. While trade association membership may predominantly consist of either MNCs or local companies, it can be difficult to present unbiased views about potential regulatory changes.

What can be learned from other industries? On the pharmaceutical side, RDPAC (R&D-Based Pharmaceutical Association Committee) has had some success as an industry association. Although at face value consisting of 38 MNC members, RDPAC has shown the

commitment to be a thought partner to China's government on its "Healthy China" agenda.

Over the years, RDPAC has taken on a number of important issues, including drug safety and quality, access to innovative medicine, and the drug innovation ecosystem, and provided valuable input to government-level discussions. This was often done by commissioning research work and international benchmarking to independent third parties, and by creating high-quality study reports that served as welcome input for regulatory decision-making.

RDPAC also embarked on partnerships with policy research organizations in China, including the Development Research Center of the State Council and the China Society of Economic Reform. Objectives of these initiatives were an assessment of health care service standards in China, and a report on strategic regulatory choices within the China essential drug system.

In summary, RDPAC provides an example of a MNC-focused organization that has succeeded in adding value to China's regulatory stakeholders through collaboration and high-quality, fact-based perspectives on topics of critical importance to the system.

Another interesting example is the work of the Bill & Melinda Gates Foundation (BMGF) in the health regulatory space. Early in 2016, BMGF signed a memorandum of understanding (MOU) with CFDA, aiming to work together on enhancing the regulatory system in China and facilitating the delivery of high-quality, safe and effective medical products to those in need in low-income countries.

Under the MOU, the foundation and the CFDA agree to support the reform and further strengthening of China's medical-product clinical trial and marketing authorization application review and approval system in an effort to promote drug accessibility; enhance compliance with internationally recognized GMPs by Chinese medical product manufacturers; support the elevation of China's regulatory capabilities and standards of medical products to international levels; and foster global regulatory collaboration to enhance global medical-product quality, safety and efficacy. Drawing on its global network and technical expertise, BMGF will assist the CFDA in establishing a mechanism for attracting international talent to CFDA for longer-term secondments to assist, as part of the current reform, in training regulatory professionals and in conducting research on global regulatory trends to support the alignment of Chinese standards and practices with international requirements.

What are the implications for China's MedTech industry? First, more can be done by leveraging industry associations and investing to build distinctive, impartial perspectives on China's tough regulatory challenges. In addition, partnerships with third parties like BMGF could be explored to expand ongoing efforts to professionalize policymaking and processes from the pharmaceutical into the MedTech arena as soon as possible.

Conclusion

Since the implementation of State Council Order No. 650, the MedTech industry has faced a series of regulatory challenges, ranging from comprehensive clinical trial requirements, streamlined product approvals and strengthened GMP audits to intensified post-market enforcement. MedTech companies need to step up efforts to cope with evolving regulatory challenges in order to stay ahead of the competitive curve. More importantly, MedTech companies should form constructive partnerships with the Chinese regulatory authorities to foster innovation and improve access to new technologies. Good precedents include the RDPAC's contribution to the "Healthy China" initiative and ongoing dialogues with Chinese think tanks, and the Bill & Melinda Gates Foundation's strategic collaboration with the China FDA on talent development.

MCKINSEY & COMPANY

Florian Then is a partner at McKinsey & Company's Shanghai office. Florian is leading McKinsey's MedTech practice in Asia.

Kevin Wu is a senior engagement manager at McKinsey & Company with a special focus on medical products.

ROPES & GRAY

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

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

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