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Empowering the Medtech Industry with Effective Regulatory Incentives

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2021 WAS A PRODUCTIVE YEAR FOR CHINA'S MEDICAL DEVICE INDUSTRY. The National Medical Products Administration ("NMPA") approved 108 medical devices to combat the COVID-19 pandemic; the drug administration published a series of supplemental rules and guidelines and actively rolled out training courses since the promulgation of the Regulations on the Supervision and Administration of Medical devices (State Council Order #739) ("Order 739"); and the Annual Report on Drug Administration Statistics (2021) showed an increase in the number of medical devices approved by the NMPA and provincial Medical Products Administration ("MPA").

Order 739 presented many regulatory incentives to the Medtech industry, but not every one of them resulted in real benefits. To brainstorm how to take advantage of these incentives, more than 60 regulatory affairs leaders from domestic and foreign medical device companies participated in the 2022 Medtech Regulatory Affairs Roundtable, jointly hosted by Ropes & Gray and McKinsey & Co. The participants had a lively discussion on topics such as registration self-testing, innovative medical device registration, manufacturing localization, real-world data ("RWD") and the Greater Bay Area ("GBA") Initiative.

The participants agreed that the promulgation of Order 739 indeed shortened the review and approval timeline. However, because of the pandemic, companies have spent more time in product type testing. Participants found it challenging to take advantage of the registration self-testing regulation, because some companies may not have in-house capability to conduct self-testing. Those others who delegated the testing to a third-party lab fear that the Center for Medical Device Evaluation ("CMDE") may challenge the testing lab's qualification. Participants have also been cautious when pursuing innovative medical device registration, manufacturing localization, real-world studies and the GBA Initiative. The intent of policy makers is encouraging and optimistic, but some unanticipated obstacles seem to deter the industry's willingness to fully execute on these opportunities.

This article is a summary of the roundtable discussion on key regulatory incentives for accelerated market access, including innovative medical device registration, manufacturing localization, real-world studies and the GBA Initiative. The participants provided the industry's recommendations for regulators' consideration.

Innovative Medical Device Registration

Order 739 was promulgated to encourage development of innovative medical devices. The number of innovative medical devices approved in 2021 increased by 35 percent over the previous year. Hundreds of innovative medical device products were approved by the NMPA. The industry accumulated valuable experience in registering innovative medical devices under the current regulatory framework. The successful precedents also prompted the industry to develop and register more innovative products, forming a healthy competitive landscape of the medical device industry to stimulate research and innovation.

According to roundtable participants, when experts evaluate if a product is innovative, they typically balance three criteria: "degree of innovation," "clinical value" and "maturity." For products with significant clinical value, there will be higher tolerance for variation of product forms and features. Another great benefit of the innovative device approval pathway is for applicants to communicate with the CMDE and reviewing experts in the early stages of product R&D to resolve technical uncertainty. Finally, manufacturers of innovative medical devices may be recognized as a high-tech company by the local government and enjoy preferential tax treatment and government subsidies.

More than half of the survey participants nonetheless stated that their companies currently do not plan to submit applications for innovative medical devices. Possible reasons include:

- **Missing key drivers for improved market access:** The innovative medical device pathway allows an accelerated review process. However, companies do not always have a tight timeline to launch their innovative products in China. Rather, they are more concerned about whether their innovative products will enjoy a competitive advantage in hospital formulary listing, medical insurance reimbursement and hospital tenders. Although Order 739 declares that innovative medical devices may receive support in terms of research grants, financing, loans, government procurement and medical insurance reimbursement, etc., the specific measures have not been implemented. Consequently, companies do not consider the current policy initiative an appealing pathway.
- **Unclear prospect for accelerated approval:** Order 739 does not set a maximum time bar for the innovative medical device registration process. It usually takes 60 business days for the CMDE to decide whether to grant an innovative medical device designation and at least another 10 business days for the public notice-and-comment process. If the review and approval process is not guaranteed for acceleration, many companies may choose not to wait for 3.5 months to be qualified as an innovative device.
- **Potential disclosure of confidential information:** The CMDE would make its technical review report publicly available once an innovative medical device receives marketing approval. Some companies worry that the technical review report may contain know-how or trade secrets and aid competitors' R&D efforts. Therefore, they may choose not to pursue the innovative medical device approval pathway.

The Industry's Reflection and Recommendations

Medical device companies have been striving to advance product research and development to more speedily introduce new technology to the market. The regulatory pathway for innovative devices is a critical means to this end. The following recommendations may help materialize this policy incentive:

- **Set the review time limit for innovative devices:** Current medical device registration rules specify a maximum review time that is equally applicable to regular devices and innovative devices. Medtech companies advocate that the CMDE consider setting a review time limit for innovative devices to truly accelerate their time to market. Alternatively, the CMDE may consider publishing the total number of days spent on technical review when the relevant innova-

tive device is approved. This can be a useful benchmark for medtech companies to assess if they would like to invest in qualifying their products for the innovative device pathway. If innovative devices can truly benefit from the fast-track review and approval process, it will surely attract more medical device companies to invest in innovation.

- **Accept variation and renewal applications under the fast track:** The CMDE may consider admitting post-approval change applications to the green channel if they are for a new intended use, a new route of administration, or new manufacturing processes that can significantly improve product safety and efficacy. In addition, products approved through the innovative device pathway may continue using the pathway when applying for registration renewal, provided that no comparable products exist on the market. Medtech companies often spend more time on registration renewal and post-approval changes compared to new product registration. Therefore, accepting variation and renewal applications under the fast track will help medtech companies optimize total product life cycle management and truly harvest the return on their R&D investment.

Manufacturing Localization

In light of the "Buy China" policy and the desire to further penetrate the Chinese market, many multinational companies have been evaluating how to relocate their manufacturing operations to China ("manufacturing localization"). Domestic companies have also been actively exploring cross-border licensing and technology transfer opportunities.

The Guideline on Localization ("Order # 104"), announced by the NMPA in 2020, stipulates the requirements for technical review, pre-approval inspection and post-market supervision of localized devices. Order # 104 simplifies the dossier requirements for localized devices, and the medtech industry welcomes this policy incentive. Approximately two-thirds of 33 medtech companies participating in our survey have a strong interest in manufacturing localization. Approximately one-half of the survey participants are preparing for a regulatory submission for manufacturing localization. However, few companies have successfully completed product registration using the abbreviated pathway under Order # 104. According to the roundtable participants, the slow momentum of manufacturing localization was mainly attributed to the following factors:

- **Rigid qualification requirements for applicants:** Under Order # 104, the domestic marketing authorization applicant should be a foreign-invested company incorporated in China by the license holder of the import device. The domestic marketing authorization applicant must hold a medical device manufacturing permit by itself and cannot leverage a contract manufacturer. The organizational structure of multinational medtech companies is often complex, and the license holder of an import device may not directly invest in or manage the operation of the domestic marketing authorization applicant. In addition, companies have different interpretations of the qualification requirements. Some believe that only the wholly owned subsidiaries of the foreign legal manufacturer are eligible domestic applicants. Others believe that eligible domestic applicants under Order # 104 can include affiliates of the foreign legal manufacturer, as long as the domestic applicant and the foreign legal manufacturer have the same parent company and have equivalent quality management systems. Due to the rigid qualification requirements of domestic applicants, many medtech companies may be preempted from pursuing manufacturing localization.
- **Limited choices for product candidates:** Order # 104 requires domestic applicants to submit registration dossiers that comply with the Guideline of Medical Device Registration, which was implemented in 2014 ("2014 Order # 43"). Domestic applicants can leverage the dossiers of the import device, such as summary description, research data and clinical

evaluation data, without producing the same technical files on the localized device. However, the import devices may have been registered and marketed for a long time, and their original application dossiers may fail to meet the most current dossier requirements. It is unclear whether and to what extent the CMDE would allow domestic applicants to reference technical data in the dossiers of longstanding import devices. The uncertainty substantially restricts medtech companies from localizing some of their mature products in China.

- **Ambiguity about equivalence of quality management system:** Under Order # 104, the domestic applicant's quality management system will need to be equivalent to the foreign legal manufacturer's, especially on raw material procurement control and manufacturing process. Companies worried that, if the local authorities' pre-approval inspections expect equivalence in these two quality management systems, the entire supply chain cannot be localized. This will not only bring potential challenges to manufacturing localization but will also diminish economic benefits conferred by the policy.

The Industry's Reflection and Recommendations

Roundtable participants advocated that the NMPA clarify these ambiguities in the existing framework governing manufacturing localization and further streamline the approval process without impairing product safety, efficacy and quality.

Clarifying qualification requirements for domestic applicants: Roundtable participants hope the NMPA will clarify the qualification requirements for the domestic applicant. Ideally, the domestic applicant can include wholly owned subsidiaries of the foreign legal manufacturer and other affiliates in the same corporate group. In addition, with the full implementation of the MAH system nationwide, the NMPA may consider allowing domestic applicants to outsource product manufacturing when holding them accountable for supervising the quality management system of contract manufacturers.

- **Simplifying registration dossier requirements:** Roundtable participants hope that the NMPA can waive the full dossier requirements for medical devices that are localized through the abbreviated pathway under Order # 104. Currently, mature medical devices can be approved if they are proven to be substantially equivalent to approved predicate devices. The same philosophy should be applicable to devices that undergo manufacturing localization. The safety and efficacy of a localized device can be assured if it is substantially equivalent to its imported counterpart. The longer an import device has been on the market, the lower the risk its localized version would present. Therefore, the NMPA can focus its review on technical data that can show substantial equivalence of the two devices. Even if the dossier of an import device does not fully adhere to the latest dossier requirements, if its localized version can demonstrate substantial equivalence to the import device and the foreign legal manufacturer's quality management system, the localized device should not be denied a marketing authorization.
- **Differentiating equivalence from consistency:** The medtech industry asks the NMPA to differentiate equivalence from consistency when evaluating if the quality management system of the domestic applicant is acceptable. If the domestic applicant establishes a quality management system that deviates from the foreign legal manufacturer's quality management system in some respects that do not compromise product safety, efficacy and quality, such deviations should be deemed acceptable.

Real-World Evidence (RWE)

Using RWD for clinical evaluation and product registration has been of great interest to the medtech industry in recent years. Several devices have been successfully approved for marketing using domestic RWE since 2020. In March 2022, two innovative devices of Boston Scientific obtained marketing approval from the NMPA using RWD collected from

Hainan pilot program. The approval process only took four months from the submission of the initial registration application. In April 2022, the CDME, together with the Hainan Provincial Medical Products Administration, issued a tentative procedural guideline that allows medtech companies to consult the regulatory authorities on how to use RWD from the Hainan pilot program in their marketing authorization applications. These examples presented a promising outlook for broader application of RWD.

The success of the Hainan RWE pilot program attracted a growing number of medtech companies to consider incorporating RWE in their clinical evaluation and registration plans. However, companies also experienced some hurdles when collecting and using RWE, specifically:

- **Using overseas RWE:** The Technical Guidelines for the Use of RWD for Clinical Evaluation of Medical Devices (Tentative) ("Tentative RWD Guidance"), effective since November 2020, outlines the relevance and reliability criteria for RWD. RWD collected in the country or region where the device has been marketed can be used as a supplement to the existing clinical evidence to support marketing authorization applications in China. However, to our knowledge, RWD used in successful precedents were all collected in the Hainan pilot zone. For example, the XEN Glaucoma Treatment System approved in 2020, the Catalys Precision Laser System approved in 2021, and the Rezūm Water Vapor Therapy equipment and its disposable prostate treatment accessory approved in 2022 all underwent a real-world study in Hainan to generate RWD. Roundtable participants mentioned that some companies tried to register products in China using RWD collected overseas but ended up relying on RWD collected domestically to obtain approval. The overseas RWD collected may not meet the CMDE's expectation for many reasons. The original data could be incomplete, because they were collected at an earlier time based on a different standard. Ethics reports may not accompany overseas RWE. These factors will make it difficult for medtech companies to meet the reliability criteria.
- **Generating RWD for domestic devices:** Currently, medical devices that have been approved using RWD are all imported products, and the RWD used so far were all collected in the Hainan pilot program. Medical devices that are in urgent clinical need but have not been approved in China can be imported to Hainan for use in designated hospitals. This makes it easier for foreign device manufacturers to collect RWD in the Hainan pilot program and use such data for marketing authorization in Mainland China. However, domestic device manufacturers are not permitted to participate in the Hainan pilot program. This prevents domestic device manufacturers from taking advantage of the RWD when seeking regulatory approvals.
- **Research infrastructure in Hainan Pilot Zone:** When high-risk medical devices are put into clinical use, patients need to continuously receive high-quality medical care to ensure their safety and health are well protected. Some medical institutions in the Hainan pilot zone may not be able to meet the GCP standards and cannot undertake clinical study site responsibilities. Beginning in 2021, several leading academic medical centers started to open their branches in the Hainan pilot zone. These academic medical centers will hopefully enhance the research infrastructure in the Hainan pilot zone.

The Industry's Reflection and Recommendations

The NMPA and the CMDE made significant accomplishments using RWD to accelerate market access of innovative devices. The medtech industry proposes the following areas for the NMPA's and the CMDE's further consideration.

- **Providing clearer guidance on using overseas RWD for regulatory filings in China:** The medtech industry hopes that overseas RWD can play a more prominent role in regulatory submissions. First, applicants may be allowed to use overseas RWD to supplement clinical trial data in support of product registration in China. Second, the CMDE may issue technical review guidelines outlining key elements of a well-designed and implemented real-world retrospective, observational study to ensure the relevancy and reliability of overseas RWD. Third, the CMDE may consider listing regions (such as regions with high ethnic similarity to Chinese patient populations, regions with a developed RWD system, etc.) and sources (such as hospital electronic medical records, medical insurance records, etc.) of overseas RWD that are more likely to be accepted by Chinese regulatory authorities.
- **Improving Transparency of Regulatory Decisions:** The medtech industry hopes that the CMDE can publish the technical review reports of approved devices using RWD as clinical evidence. Also, medtech companies expect the CMDE can allow more consultation opportunities in relation to RWD, similar to the consultation channels available in the Hainan pilot zone. In practice, the development of a real-world study may require years of planning. Early engagement with the regulatory authorities and learning from the technical review reports of approved products will greatly help companies optimize the design of real-world studies and enhance the likelihood of success.

The Greater Bay Area Initiative

The GBA Initiative permits the clinical use of Hong Kong- or Macao-marketed drugs and medical devices in designated pilot hospitals in the GBA without prior NMPA marketing authorization, provided that such products have been used in public hospitals of Hong Kong or Macao and have clinical urgency and therapeutic superiority. In 2020, the NMPA published a series of guidelines on the GBA Initiative. As of April 2022, six medical devices addressing urgent clinical needs have been introduced under the Initiative. In addition, the number of designated pilot hospitals has increased from one to five, spreading across the GBA.

Roundtable participants believe that the GBA Initiative allows eligible products to gain an advantage in market entry because they can enter designated hospitals before being approved for marketing in China. Manufacturers of the eligible products may also use the RWD collected from such designated hospitals to support clinical evaluation for product registration in China. Furthermore, The GBA Initiative has its unique value proposition and is attractive to both foreign and domestic medical device companies. Unlike the Hainan pilot program, which is only open for devices approved in the EU, U.S. and Japan, the GBA Initiative does not rule out domestic medical devices. Domestic products can thus use this pathway to expedite its access to the Chinese market.

Notably, more than half of the 33 survey participants stated that they did not plan to take advantage of the GBA Initiative. Roundtable participants identified a few reasons:

- **Concerns over disclosure of pricing information**: Medtech companies are concerned that they might be required to disclose commercially sensitive information, such as supply price in Hong Kong and Macao public hospitals, in order to demonstrate that the devices have been listed in the hospital formulary. This may limit medtech companies' price negotiation leverage with the GBA-designated hospitals. The GBA Initiative is a double-edged sword: it brings a market entry advantage, but it also imposes potential pricing restrictions. Companies may have to conduct a risk-benefit analysis when deciding whether to participate in the GBA Initiative.

- **Compliance risks relating to promotion of unapproved products:** Accelerating product launch in Mainland China is a driving force for some medtech companies to participate in the GBA Initiative. However, current regulations remain silent on how to legitimately promote these unapproved devices at designated hospitals. Under the current advertising regulations for medical devices, contents of device advertisements must be examined and approved by provincial MPAs before they can be released. Such review and approval will focus on conformity with the registration certificate and NMPA-approved labels. Since devices admitted to the GBA-designated hospitals will not yet be unapproved by the NMPA, medtech companies will not be able to obtain clearance for their promotional materials.
- **Limited clinical capacity at designated hospitals:** Currently, the five designated hospitals do not have a full coverage of clinical services. As a result, some companies decided not to take part in the GBA Initiative because they could not find a pilot hospital that had a suitable clinical specialty area for their products.

The Industry's Reflection and Recommendations

To materialize benefits created by the GBA Initiative, roundtable participants identified the following issues for the NMPA's further consideration:

- **Allowing the redaction of commercially sensitive information:** The NMPA may consider allowing companies to redact commercially sensitive information when proving that the products have been procured by public hospitals in Hong Kong and Macau. This will certainly eliminate concerns about losing pricing autonomy in the GBA as well as the rest of China.
- **Modifying existing regulations to legitimize product promotion:** The NMPA may consider modifying the requirement for device promotion to enable dissemination of product-related sales and marketing materials at GBA-designated hospitals. The GBA Initiative is appealing to the medtech industry because it offers an early-access opportunity for unapproved devices. Medtech companies need to educate healthcare professionals and patients on the correct use of the unapproved devices. To the extent that the information contained in the promotional materials is true, complete and accurate, the NMPA may consider waiving the content review requirement for promotional materials that will only be used at the GBA-designated hospitals.
- **Diversifying the clinical infrastructure at GBA-designated hospitals:** The NMPA may consider adding additional pilot hospitals to fill the gap in clinical infrastructure, especially specialty hospitals that target critical illnesses or high-risk medical practice areas. Medtech companies will only be able to enlist more and more new products under the GBA Initiative when the clinical infrastructure can meet a diversified disease portfolio.

CONCLUSION

NMPA Deputy Commissioner Mr. Jinghe Xu stated in early 2022 at the China Medical Device Regulatory Affairs Conference that the medical device industry is entering its golden age. At this critical juncture, medtech companies and the NMPA should share the common goal to promote innovation and healthy development of the industry.

Medtech companies acknowledged the NMPA's strong desire to introduce and implement regulatory incentives that can induce innovation and accelerate market access. These policies send a promising signal to medtech companies operating in China, despite growing uncertainty in the global economy and the persistent pandemic. With the NMPA's unwavering determination to cement regulatory reform, we are optimistic that the Chinese medtech industry can be empowered to advance to the next level.

CONTACTS

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