Guest article

Successful approval of medical products in China – a road with many obstacles

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The approval of medical products in China starts with their classification following the Medical Device Classification Catalogue, the current version of which was published on 31 August 2017 by the China Food and Drug Administration (CFDA). This catalogue is clearly illustrated with a large number of examples. If a device cannot be unequivocally classified into one of the 22 specified product categories, the Rules for Medical Device Classification are to be used. In borderline cases, there exists the option of applying for official qualification with the National Medical Products Administration (NMPA, formerly CFDA). Potential risks, specific characteristics, and the use of the device must be described in the application. The producer must submit a detailed functional description and proof of classification of the device in the producer's country of origin together with the application.

It can take months to process applications. China uses the three risk classes I, II, and III for medical technology and in-vitro diagnostics (IVD). European classifications merely serve as an indication for the class, with Chinese officials very frequently reaching a different classification. If this is the case, the European products are usually assigned one class higher. If the device is assigned to risk class II or III, the next step of the registration process comprises the creation of the Technical Requirements (formerly: Registration Standard), which map out the requirement to agree on type tests with a Chinese test laboratory. Active medical devices are subject to performance, electrical safety, and electromagnetic compatibility (EMC) inspections in China. China has its own system of standardisation. Obligatory Chinese standards are called GuoBiao (GB), which is literally translated as "national standard". Chinese industry standards for medical devices are called YY standards. The test standard for electrical safety is called GB 9706.1-2007. It is based on IEC 60601-1: 1988, 2005, 2012. The standards are equivalent but not completely equal. The test standard for EMC in China is YY 0505-2012 and is identical to IEC 60601-1-2: 2004. Nevertheless, tests must be carried out at a test laboratory accredited by the NMPA in China. In China, biocompatibility tests for devices which come into contact with the patient's body are carried out in accordance with GB/T 16886.1-2011, which is in turn identical to ISO 10993-1:2009. Here, there exists the opportunity of having a test which was carried out abroad recognised if the test was performed in accordance with ISO 10993-1:2009 and the test report issued was by a test laboratory approved following Good Laboratory Practices (GLP).

Preparation of the application dossier can begin in parallel to the type tests. The type test reports and the Clinical Evaluation Report (CER) are the cornerstones of the application. Whether a clinical trial in China is required for the CER can be determined using various exclusion criteria. The NMPA has published multiple lists of medical products and IVD of Classes II and III which do not require clinical trials in China for registration. The third version of the Exception List is already available for medical technology, as is the second extended version for IVD. These lists comprise 855 exempted medical devices and 393 exempted IVD products for which a highly simplified CER suffices on application.

In other instances, clinical data which were collected in a clinical trial performed outside of China can be used to create the CER if these meet Chines rules. If such data are not available, there still is the option of finding a predicate device approved in China and use its data. The applicant must have obtained the

clinical data in a legal manner. A clinical trial for the product is only unavoidable if these three approaches are fruitless.

Class I medical products don't need to be put to a type test or undergo a clinical trial in China; for these, simple notification of the NMPA suffices.

The guidelines on technical lifetime examination, updated on 14 May 2019, form a new challenge in the registration of active medical products. As part of the registration process, applicants must prove the lifetime of their products. Here, the lifetime is the period during which safe operation of the product is guaranteed.

Under the NMPA provisions, only a legal person with residency in China can apply for the registration of medical technology devices. For the registration of their products, foreign producers thus require a legal representative, the NMPA Legal Agent. The producer must issue a written power of attorney for representation at the NMPA. The NMPA Legal Agent plays a decisive role in applying for, changing, and extending certificates as well as importing devices to China. Therefore, this position should be selected carefully, with the most important decision criteria being experience in dealing with regulatory matters, the relevant product standards, and the competent authorities. There are generally three options available:

» 1. The Chinese subsidiary of the producer assumes the function of legal agent.
» 2. The distributor is appointed as the legal agent; in this case, however, a company is to a large extent dependent on the distributor, who is virtually given exclusivity.
» 3. A consultancy company responsible for the NMPA registration is appointed as the NMPA Legal Agent. This has the advantage of remaining independent and being able to use as many distributors as required, as well as change them.

On 7 May 2019, the Center for Medical Device Evaluation (CMDE) announced the introduction of an electronic platform to submit the application dossier (http://erps.cmde.org.cn). The system serves electronically managed medical product registrations; in future, all documents for the NMPA registration are to be submitted through this eRPS system, with the paper form no longer being necessary.

Since 10 May 2019, it is thus possible to apply for a Certificate Authority (CA). The CA certificate is required to log into the eRPS system. With imported medical products, the NMPA Legal Agent must apply for a CA certificate on behalf of the foreign producer.

The application dossier is to be submitted in complete form, together with all accompanying documents such as test reports, certificates, evidence, etc., in Chinese.

The National Medical Products Administration checks the submitted documents for compliance with the formal requirements within a week. For Class II products, the CMDE requires approximately 60 working days for the technical evaluation of the documents and 90 working days for Class III products. After this initial technical evaluation, the NMPA expert issues a Supplementary Notice. In response to this notice, the producer must make all supplementary documents available within a year and submit these to the NMPA. Then follows the final technical evaluation, which will again take around 60 working days. The NMPA requires another 30 working days for administrative approval of the registration and to issue the certificate.

Certificates for Class II and III medical products are valid for five years. Certificate extensions must be applied for at least six months before the expiration date at the latest. There is no expiration date for certificates for Class I products.

To safeguard product quality in the life science sector, the NMPA expects proactive cooperation of the local legal representative of foreign producers. The NMPA published a guideline on responsibilities – the Guideline for Imported Medical Device Legal Agent. This includes supporting the producer in the approval of its products and regulation-compliant Chinese operating instructions. From 1 January 2019, the Chinese company name of all imported Class II and III medical products must be included in the Chinese operating instructions and on the Chinese label, and the name must match the name on the NMPA certificate. This request is illustrative of the importance of a well-informed, proactive, and cooperative NMPA Legal Agent for the timely implementation of current regulations in China. Further responsibilities of the legal representative comprise monitoring and reporting adverse events in China as well as notifying the supervisory authorities and supporting the supervisory authorities in quality control.

To this end, the NMPA has released Decree No. 1 on the reporting of adverse events for medical products on 31 August 2018. The Decree states that adverse events that occur overseas must be reported to the NMPA, and a report must be created by the local legal representative in China. This regulation assigns the responsibility for controlling, proactive monitoring, and providing information on quality problems to the producer and the NMPA Legal Agent in equal parts. The system serves to improve risk management of medical products by targeting the monitoring, evaluation, and remedying of adverse events for this product group. The NMPA Legal Agent plays a much more important role than before. As the local legal representative, they are responsible for meeting requirements after the product is brought to market, without the producer having to establish its own Chinese office.

With regards to the issue of adverse events, the State Administration of Market Regulation (SAMR) published a joint declaration together with the General Administration of Customs of China (GACC) on 30 October 2018, announcing closer cooperation in the recall of defective imported goods. With this reform, the SAMR was given the main responsibility for product recalls in China, with greater focus placed on life science products and foodstuffs, such as medical products, medicines, and cosmetics, in addition to health food and infant milk. The GACC reports to

Guest article

the SAMR on products identified as defective during the customs inspection. The SAMR in turn informs the GACC on infringements in the event of recalls, to allow the GACC to initiate measures against the involved companies. Moreover, producers and consumers can find information about recalls on the website of SAMR. The WeChat Messenger services of the SAMR and GACC also regularly publish information on recalls.

Further reinforcement of product safety controls was enacted in the Directive on the Administration of Medical Products and Medicine Overseas, passed on 28 December 2018. This regulation specifies that the NMPA will also carry out factory inspections for producers in other countries in the future, to guarantee the safety and effectiveness of imported medical products and medicines.

Comprehensive inspection of all producers is not envisioned; sampling will take place on the basis of risk assessments. To date, primarily Chinese producers were regularly inspected. In January and March 2019, the production sites of 24 foreign companies were already subjected to an inspection. Deficiencies were identified in all instances. The respective problems can be looked up online on the NMPA website. Producers then have 50 working days to take corrective measures.

On 23 August 2020, the NMPA announced the introduction of the UDI system (Unique Device Identification) for medical products in China. The new UDI regulation took effect on 1 October 2019. This important requirement will already affect the registration and import of medical products in China in the very near future. To date, four important documents have been published on the UDI (NMPA Announcement on Issuing the Rule of UDI System for Medical Devices, Rule for UDI System of Medical Devices in China, YY/T 1630-2018 Fundamental Requirements for the UDI and the NMPA UDI Interpretation Rule). Foreign producers of medical products must carry out the following steps:

- 1. Creation of a DI code (Device Identification) in line with the UDI code standard of the Chinese approval authority ANCC (Article Numbering Center of China) and determining the PI code structure (Production Identification)
- 2. From 1 October 2019, the applicant must submit the relevant DI code to the NMPA for applications for approval of medical products – such as new approvals, renewed approvals, and changes to the approval of medical products.
- 3. Selection of a suitable data carrier – such as a barcode, QR code, or RFID code – in accordance with the ANCC Standard and applying it to the product or packaging.
- 4. Uploading the DI code and the associated information to the UDI database for medical products before the product is imported to China. Important – this UDI database has not yet been made available by the NMPA.
- 5. If there are changes to the DI code and the associated information, the applicant must update the information in the UDI database.

Major regulatory challenges must be overcome to enter the Chinese market. Therefore, companies should schedule plenty of time and arrange for an appropriate budget. After successfully going through the required tests and creating a solid application dossier, the path into this very promising market is wide open.