RegIntA
FOR YOUR COMPLIANCE

ORPHAN DEVICES & NICHE PRODUCTS

Global Approaches

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1. Summary

The European Medical Devices Regulation (EU) 2017/745 (MDR) obliges all manufacturers of medical devices to ensure that the products they place on the European market comply with the more stringent requirements of the MDR compared to the directives latest by 26 May 2024. No exceptions are allowed.

A challenge, especially for small and medium-sized enterprises (SMEs), is the required data collection for clinical evaluation. In the case of niche products with only a small production volume, the considerable costs involved in meeting the MDR requirements are often not worthwhile. If the manufacturer does not want to jeopardize the existence of his company, he often has no choice but to cease production. In this way, important and well-established medical devices disappear from the market, resulting in supply bottlenecks for patients.

The BVMed advocates exemptions for so-called orphan devices and niche products in order to support SMEs in particular. A proposal is currently being drafted, which will be submitted to the newly created MDCG task force for review. RegIntA has therefore researched regulations for orphan devices and niche products and support for SMEs in key global markets. The comparison includes the following countries: Australia, Brazil, Canada, China, Japan, and the United States.

As our research shows, the countries' approaches are completely different. Interestingly, the issues faced by manufacturers and therefore patients of orphan devices and niche products have not yet reached the established Western authorities. Hardly any support is provided by them. An exception is the USA with the special registration path of the Humanitarian Device Exemption. In contrast, Japan and China offer a number of facilitations to manufacturers, ranging from special registration pathways and adapted clinical evaluation to fee reductions and certain support programs. It should be noted, however, that all of these authorities expect the medical device to meet the country-specific definition of an orphan device.

In sum, there is much potential in these approaches that can serve as a basis for future facilitation of orphan and niche device manufacturers in the European Union.

2. Country Overview

	Australia	Brazil	China	Japan	Canada	USA
Is there a separate registration pathway for orphan devices or niche products?	No	No	Yes, within the Priority Approval Procedure	There is no dedicated registration pathway, but there is a dedicated orphan system that prioritizes registration.	No	Yes: Humanitarian Device Exemption (HDE)
Are there further options?	Yes, as an exception outside the ARTG for physicians.	Yes, via the Compassionate Use Program	Yes, through the special imports of "Hainan registration" and Guangdong Hong Kong-Macau access to medicines and medical devices"	This is already covered with the Orphan Device System	Yes, via the Priority Review or Special Access Program	Yes, via further registration paths if the HDE criteria are not met
Are manufacturers of orphan devices or niche products financially supported?	No	No	No	Yes, orphan device manufacturers	No	Yes, through OOPD programs
Can the requirements for the clinical	No, the requirements are based on the TGA	No, the requirements of the Brazilian	Only if it is an orphan device as defined in NMPA	Yes, according to Notification 0329	No	Compared to traditional PMA - yes.

	Australia	Brazil	China	Japan	Canada	USA
evaluation be reduced if the product has been in use for many years?	conformity assessment or the European conformity assessment.	regulations are based on the risk class.	Notification No. 2018-101	No. 1, 29 March 2013		
Are there special funding programs for medical device manufacturers?	Not from the TGA. However, there are numerous funding opportunities for MedTech companies through the Australian government.	No	No	Yes	Funding programs are not specific to medical devices	Yes, through OOPD programs
Are there special rates for SMEs?	No	Yes	Yes	No, but there are fee reductions for Orphan Devices	Yes	Yes

2.1. Australia

The Australian regulations for medical devices are based on the requirements of the European directives and - since the Date of Application – on the MDR regulation. This has created the conditions to accept the European conformity assessment as equivalent and to allow free trade between the European Union and Australia. With the introduction of the MDR, further adjustments were necessary. But as in the MDR, the Australian requirements do not (yet) include a concept for orphan devices or niche products. Only the approval of so-called orphan drugs for rare diseases is encouraged.

As confirmed by the Australian Therapeutic Goods Administration (TGA), Australian medical device regulations do not consider orphan device categorization. In most cases where medical device regulations change, manufacturers may be granted transition periods, but all devices must have the same level of regulatory compliance.

There is no separate registration pathway for orphan devices or niche products. In principle, all products sold in Australia must be included in the Australian Register of Therapeutic Goods (ARTG) after successful conformity assessment. Exceptions apply, for example, to patients or healthcare professionals to ensure the care of the relevant patients. A physician may dispense the product directly to specific patients he or she treats without requiring separate approval for individual patients. To do so, the physician must report the number of patients treated every 6 months. Use of the product must be reported to the TGA twice a year, for each period from January 01 to June 30 and July 01 to December 31. Alternatively, medical professionals can apply through the Special Access Scheme (SAS) for named patients to import medical devices that are not in the ARTG.

Australia also does not provide an option to reduce the clinical evaluation requirements for medical devices that have been proven to treat patients for many years. Under the Therapeutic Goods (Medical Devices) Regulations 2002, the different requirements are primarily based on risk classes.

Although MedTech companies are not supported by the TGA, they are offered the opportunity to receive financial support from the Australian government. For example, there are CSIRO Innovation Funds which primarily support SMEs and startups in commercializing innovations. Developments that address important health challenges are funded by the BioMedTech Horizons (BMTH) program. An overview of the funding programs can be found on the TGA website "Useful resources for business and researchers."

In addition, the "National Strategic Action Plan for Rare Diseases" was published in 2020, which generally describes the need to create a policy to address the issues faced by those affected by orphan diseases. However, there are no proposals for practical implementation, in particular how the supply of patients with corresponding medical devices can be guaranteed.

2.2. Brazil

Brazil, as a founding IMDRF member and ICH member state, has a leading role, especially for Latin America, but also beyond.

Access to effective drug therapies for rare diseases is an important issue for the Brazilian agency ANVISA. Thus, every year on International Orphan Diseases Day, February 28, the current state of medical care for affected patients is highlighted and new developments are pointed out. However, the focus is solely on the pharmaceutical sector.

In general, all medical devices require registration via the Registro or Notificação registration pathway, depending on their risk class. However, exceptions are possible. On the one hand, these products are listed on ANVISA's website. On the other hand, there is the possibility to give patients access to medical devices that are still in development and for which there are no therapeutic alternatives. For this purpose, Resolution RDC No. 608/2022 established the Compassionate Use Program, which is described in the Guidance on the Compassionate Use Program dated 04 March 2022. However, there is no specific registration pathway for orphan devices or niche products.

Even though there are no funding programs available in Brazil for manufacturers of orphan devices or niche products, the complex fee schedule under Resolution No. 198/2017 provides an opportunity, especially for SMEs, to reduce the costs charged by ANVISA. Cost reductions are only possible if annual sales are proven. A large company is considered to be one that has revenues in excess of 50,000,000 Real (about 9.5 million EUR). For medium-sized companies in Group III, the limit is 20,000,000 Real (about 3.8 million EUR). The largest cost reduction is for "small entrepreneurs" who earn the same or less than 360,000 Real (about 68 400 EUR) per year. More information on how the different company sizes are grouped can be found on ANVISA's website. The Brazilian fee schedule of all products regulated by ANVISA is published in Resolution RDC No. 198/2017.

2.3. China

China is one step ahead of Europe. Currently, 121 diseases are recognized as orphan diseases. Under the "Priority Approval Procedure", medical devices used for the diagnosis or therapy of rare diseases can receive accelerated approval. Products that are specially made for elderly patients or children, or medical devices for which there is an urgent need but no comparable product on the market are also eligible for this procedure.

For the "Priority Approval Procedure", a complete registration application is first submitted to the National Medical Administration (NMPA) through standard means. Once the application is accepted, the applicant may submit a second application for the "Priority Approval Procedure" to expedite NMPA's review and approval. At the monthly meeting of the Center for Medical Device Evaluation (CMDE) Expert Committee, all formally correct applications are discussed. The committee's decision is published no later than five working days. If there are no objections, the product is approved for expedited registration. In comparison, the review-only

process for standard registration takes sixty working days for Class II medical devices and ninety working days for Class III medical devices.

It is important to understand that the "Priority Approval Procedure" basically has the same requirements, including Clinical Evaluation, as the standard approval process.

It is insightful to refer to NMPA Notification No. 2018-101, the Guidelines on Registration Review of Medical Devices for the Prevention and Treatment of Orphan Diseases, dated 12 Oct 2018. The Guideline applies exclusively to the prophylaxis, diagnosis and treatment of orphan diseases published in the Joint List of the National Health Commission, the Ministry of Science and Technology, the Ministry of Industry and Information Technology, the State Drug Administration and the State Administration of Traditional Chinese Medicine.

The NMPA Notification No. 2018-101 sets out the requirements for orphan device documents to be submitted, including the clinical trial exemption principles.

Clinical trial exemption principles are:

- The company should submit evidence to the technical review department that sufficient preclinical studies have been conducted or that there is other evidence that the benefits of using the device clearly outweigh the risks.
- For medical devices (excluding in vitro diagnostic reagents) for which comparable products are on the Chinese market, the safety and efficacy of their clinical use may be evaluated by the equivalence principle.
- The clinical evaluation for medical devices based on overseas data can be accepted during registration if they comply with the "Technical Guidelines for the Acceptance of Overseas Clinical Trial Data of Medical Devices". If, during the evaluation process, the review department concludes that it is not necessary to conduct additional clinical trials in China before marketing the device, the device may be exempted from clinical trials.

The Chinese government generally encourages the registration of innovative medical devices. There is also a separate registration route for this.

In the context of innovative products, it is also necessary to refer to the "Hainan Registration" and the "Guangdong Hong Kong-Macau Access to Medicines and Medical Devices".

The "Hainan Registration" is actually a special import permit introduced in 2013 for medical devices that are urgently needed in China and is restricted to the Boao Lecheng International Medical Tourism Pilot Zone Free Trade Port in the Hainan Province. The medical devices manufactured by foreign manufacturers outside China, which are already approved by the authorities of the country of origin, can be imported without NMPA registration and used in the designated medical facilities within the pilot zone. The clinical data obtained from use in the pilot zone can be used as additional evidence for registration of the medical device with NMPA, which may have the advantage of expediting the registration process. These clinical data are also referred to as real-word data and include hospital data, insurance data, or regional registration data, among others.

The overall goal of the "Guangdong Hong Kong-Macau Access to Medicines and Medical Devices" is to make it easier for Hong Kong and Macau residents to obtain medical care in mainland China. At the same time, Chinese patients will have access to medical devices approved in Hong Kong and Macau that do not have NMPA registration. This is especially relevant to medical devices for the treatment of orphan diseases. The import permit for importing the products from Hong Kong or Macau to mainland China is available after 35 working days after application and is free of charge.

In principle, the NMPA grants fee reductions to SMEs if the relevant proof is provided. Whether a company is recognized as an SME depends on its turnover and number of employees.

2.4. Japan

The Japanese Ministry of Health (MHLW) has taken special support measures to ensure the medical supply of the population suffering from a rare disease with appropriate drugs, but also with regenerative therapies and medical devices. In this context, only a disease that meets the defined criteria is considered an orphan disease. These criteria include the number of patients affected, medical necessity due to the unavailability of a comparable product, and the development potential of the product.

The following measures have been taken by the government:

- Grants can be applied for through the National Institute of Biomedical Innovation, Health and Nutrition (NIBIO). The goal is to reduce the costs associated with the development of drugs, regenerative therapies and medical devices for rare diseases.
- The Japanese Pharmaceutical and Medical Devices Agency (PMDA) and the National Institute of Biomedical Innovation, Health and Nutrition provide assistance and advice on clinical trials and research for rare diseases products. Consultation are also less expensive than compared to traditional products.
- Within the context of tax relief up to 20% of the expenses for research and clinical trials of drugs, regenerative therapies and medical devices for orphan diseases can be deducted.
- To ensure that drugs, regenerative therapies and medical devices for orphan diseases are available as soon as possible, they are given priority over other products in the approval process. Regulatory fees are also lower than for ordinary products.
- For drugs, regenerative therapies, and medical devices approved for orphan diseases, the period for reexamination of the approval is extended to a maximum of ten years. In comparison, registration for conventional medical devices must be renewed every five years.

Before a medical device is recognized as an orphan device, consultation with the MHLW is required. An official application is then submitted. The MHLW informs the applicant of the decision after all application forms have been reviewed.

The MHLW published a list of approved orphan devices on the website (as of 2020).

With respect to the required clinical evaluation data for orphan devices, Notification 0329 No. 1, dated 29 Mar 2013, was published. According to this document, a task force was established back in February 2012 to engage in dialogue with the MedTech industry to find a practical approach to handling clinical trial data for orphan devices. The PMDA emphasizes that when considering the approval of a medical device, it is important to comprehensively assess the benefit-risk ratio of the device, including the severity of the disease and comparison with existing therapies. However, the agency acknowledges that it is often difficult to conduct clinical trials for rare disease medical devices because the number of subjects is small. Therefore, after consultation with PMDA, clinical trials may be waived in following cases where a scientific evaluation is possible based on the efficacy and safety data already collected:

- The medical device is already approved for the intended use in question by a health authority recognized as equivalent to the Japanese authority (e.g. FDA), and it has been used there as medical treatment for some time, and the equivalent authority reviewed the same data for testing.
- The medical device is already approved for the intended use in another country and has been used in medical treatment there for some time and is the subject of a scientific paper published in an internationally recognized journal or a technical article evaluated by an international organization.
- Test results are available that confirm the ethics, scientificity, and reliability of the application, such as in studies commissioned as part of a public research project or conducted as an advanced medical treatment.
- The application for approval involves a change to a previously approved orphan device that is intended to significantly improve the safety of the device. As the device is intended for only a very limited number of individuals, this makes it difficult to conduct a clinical trial.

Notification 0329 No. 1 also indicates that post-market surveillance measures need to be strengthened due to the reduced data available for the clinical evaluation. The manufacturer/distributor must conduct post-market surveillance of the efficacy and safety of the product. To this end, he should register patients using the product, if necessary, collect efficacy and safety data, and use these data for safety measures. In addition, it may be necessary to establish requirements for medical use in cooperation with academic societies and associations. Also, it cannot be ruled out that unforeseen problems may arise after the device is placed on the market due to the small number of patients evaluated in the clinical trials, etc. Therefore, the manufacturer of the medical device is required to inform patients and healthcare professionals that the number of patients evaluated in "clinical trials, etc." is small and the possibility of unforeseen problems occurring after marketing cannot be ruled out.

2.5. Canada

Currently, there is no concept for orphan devices or niche products in Canada.

In response to inquiries, the Canadian authority Health Canada referred to the possibility of Priority Review. The applicant can indicate in the marketing authorization application whether

a Priority Review is requested. This option applies only to Class III and IV medical devices intended for the diagnosis or treatment of a serious, life-threatening or seriously debilitating disease. There must be no comparable product approved in the Canadian marketplace, or it must represent a significant improvement in the benefit-risk profile compared to available medical devices. Specifically, Priority Review is intended to treat rare or high-risk diseases (e.g., diabetes, heart disease, cancer) or vulnerable patient populations (e.g., children and adolescents, people with disabilities, or the mentally ill).

Applicants will be notified if their Priority Review application has been accepted when the request is received. Priority Reviews are reviewed on an expedited basis within fifteen days. The same clinical data is expected to be submitted for standard registration. There is also no reduction in fees.

As an alternative to the Priority Review, medical devices can be imported and sold for named patients through the Special Access Program in emergency situations, or when no comparable therapies are available. All risk classes are covered under this option, as are custom devices.

Generally, fee reductions are available for small businesses, publicly funded health care facilities, and government organizations. A small business is defined as a company that, including its subsidiaries, has fewer than 100 employees or has annual gross sales of between CAD 30,000 and CAD 5 million (about 22,000 EUR and 3667,382 EUR).

In addition, the Canadian government provides advisory and financial support for projects related to research and development, innovation and commercialization. However, this support does not apply to specific products, or even to medical devices in general.

It is worth noting that even orphan drugs are not covered in Canadian regulations. The Health Canada website only refers to existing support in this context, which is also available for the approval of other drugs.

2.6. USA

The FDA Office of Orphan Products Development (OOPD) was established to advance the review and development of products, such as medical devices, that show promise for the diagnosis and/or treatment of rare diseases.

One of the projects of the OOPD is the introduction of a dedicated registration pathway for orphan devices. Back in 1990, the Humanitarian Device Exemption (HDE) was created in the U.S. for so-called Humanitarian Use Devices (HUDs) to encourage the development of products for small/rare patient populations.

HUDs are defined as medical devices intended for the treatment or diagnosis of diseases that do not affect more than 8,000 individuals in the United States per year.

The HDE application is similar to the Pre-Market Approval (PMA) application, but is exempt from efficacy requirements. All that must be shown is that there is a probable health benefit

and that the probable benefit outweighs the risk of injury or illness caused by the product. In addition, an HDE application receives priority processing. The review takes only 75 calendar days instead of the 180 calendar days for an ordinary PMA. In addition, there are no fees for the applicant.

Alternatively, other registration paths - depending on the product - may be available to the manufacturer if the HDE definition is not applicable, such as the Premarket Notification 510(k), which demonstrates equivalence to a Predicate Device already on the U.S. market, or the De Novo Request, which allows reclassification for new medical devices that cannot demonstrate a Predicate Device.

OPPD also offers the opportunity to apply for funds for clinical trials through the Orphan Product Grants Program.

In addition to the HDE registration fee waiver, a substantial reduction in most FDA fees is generally available for companies that are classified as a small business. A small business is defined as one that did not generate more than USD 100 million (approx. EUR 91 million) during the last fiscal year.

3. References

Australia

- Email communication with the TGA, dated 14 Jun 2022
- Therapeutic Goods Act 1989, No. 21, 1990, Chapter 4 -Medical Devices
- Therapeutic Goods Regulations 1990, Statutory Rules No. 394, 1990 Made Under the Therapeutic Goods Act 1989
- Therapeutic Goods (Medical Devices) Regulations 2002, Statutory Rules No. 236, 202, Made Under the Therapeutic Goods Act 1989

Brazil

- Resolution RDC No. 608/2022
- Guidance on the compassionate use program for medical devices
- Resolution RDC No. 185/2001
- Resolution RDC No. 40/2015
- Resolution RDC No 270/2019
- Resolution RDC 423/2020
- Health products catalog, dated 07 Jun 2022

China

- State Council Order No. 739, Regulations on Supervision and Administration of Medical Devices, 09 Feb 2021, effective from 01 Jun 2021 (repeals State Council Order No. 680 of 04 May 2017)
- SAMR Order No. 47, Administrative Measures for Registration and Filing of Medical Devices, 26 Aug 2021, effective from 01 Oct 2021 (repeals CFDA Decree No. 4 of 30 Jul 2014)
- NMPA Notification No. 2018-101, Guidelines on Registration Review of Medical Devices for the Prevention and Treatment of Orphan Diseases, 12 Oct 2018
- CFDA Announcement No. 2016-168, Priority Approval Procedure for Medical Device Registration, 25 Oct 2016
- Interpretation on CFDA Announcement No. 2016-168
- CFDA Notification No. 2017-28, Guidance on Application Dossier Preparation for Priority Approval Procedure of Medical Device Registration, 15 Feb 2017
- NMPA Notification No. 2018-101, Guidelines on Registration Review of Medical Devices for the Prevention and Treatment of Orphan Diseases, 12 Oct 2018
- Website: Q&A for consultation on the guiding principles of registration and review of medical devices used for the prevention and treatment of rare diseases, 09 Apr 2021
- NHC Notice No. 2018-10, First Batch of Orphan Disease Catalogue, 11 May 2018
- Interpretation of First Batch of Orphan Disease Catalogue, 08 Jun 2018
- Notice of State Council Office No. 2017-42, Opinions on deepening the reform of the review and approval system to encourage innovation in drugs and medical devices, 08 Oct 2017
- Website: Make every effort to promote the continuous improvement of rare disease policy ecology, 28 Feb 2022
- Website: Letter on Reply to Proposal No. 1844 (Medical Sports No. 097) of the Fourth Session of the Thirteenth National Committee of the Chinese People's Political Consultative Conference, 09 Feb 2022
- Journal article: Policy of rare diseases: International experience and its implication for China, 2018
- Opinions on Deepening the Reform of the Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices, 08 Oct 2017

Japan

- Email communication with the PMDA, dated 07 Jun 2022
- MHLW Website: Overview of the Orphan Drug and Orphan Device Recognition System (Japanese)
- MHLW Website: Overview of the Orphan Drug and Orphan Device Recognition System (English)
- Application form for orphan device designation
- Notification 0329 No. 1, 29 Mar 2013

Canada

- Email communication with the PMDA, dated 16 Jun 2022
- Medical Devices Regulations, SOR/98-282, last amended on 23 Dec 2021

- Regulations Amending the Food and Drug Regulations and the Medical Devices Regulations (Post-market Surveillance of Medical Devices): SOR/2020-262, effective from 23 Jun 2021
- Guidance on How to Complete the Application for a new Medical Device License, 22 Mar 2021
- Guidance Document: Guidance on Supporting Evidence to Be Provided for New and Amended License Applications for Class III and Class IV Medical Devices, Not Including In Vitro Diagnostic Devices (IVDDs)

USA

- Code of Federal Regulations (CFR) Title 21
- Guidance for Industry, Food and Drug Administration Staff: Humanitarian Device Exemption (HDE) Program, 06 Sep 2019
- FDA Website: Developing Products for Rare Diseases & Conditions
- Guidance for Industry, Food and Drug Administration Staff and Foreign Governments: Medical Device User Fee Small Business Qualification and Certification, 01 Aug 2018