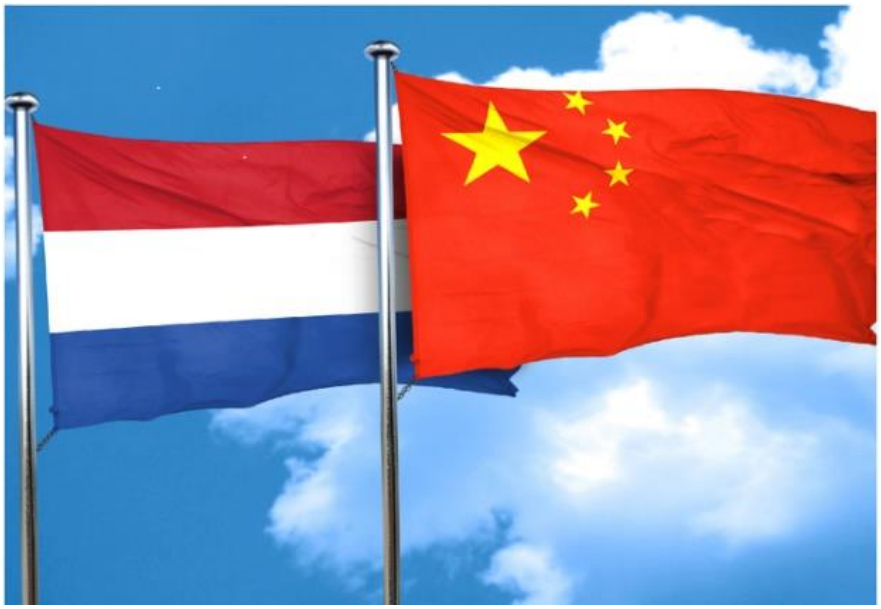
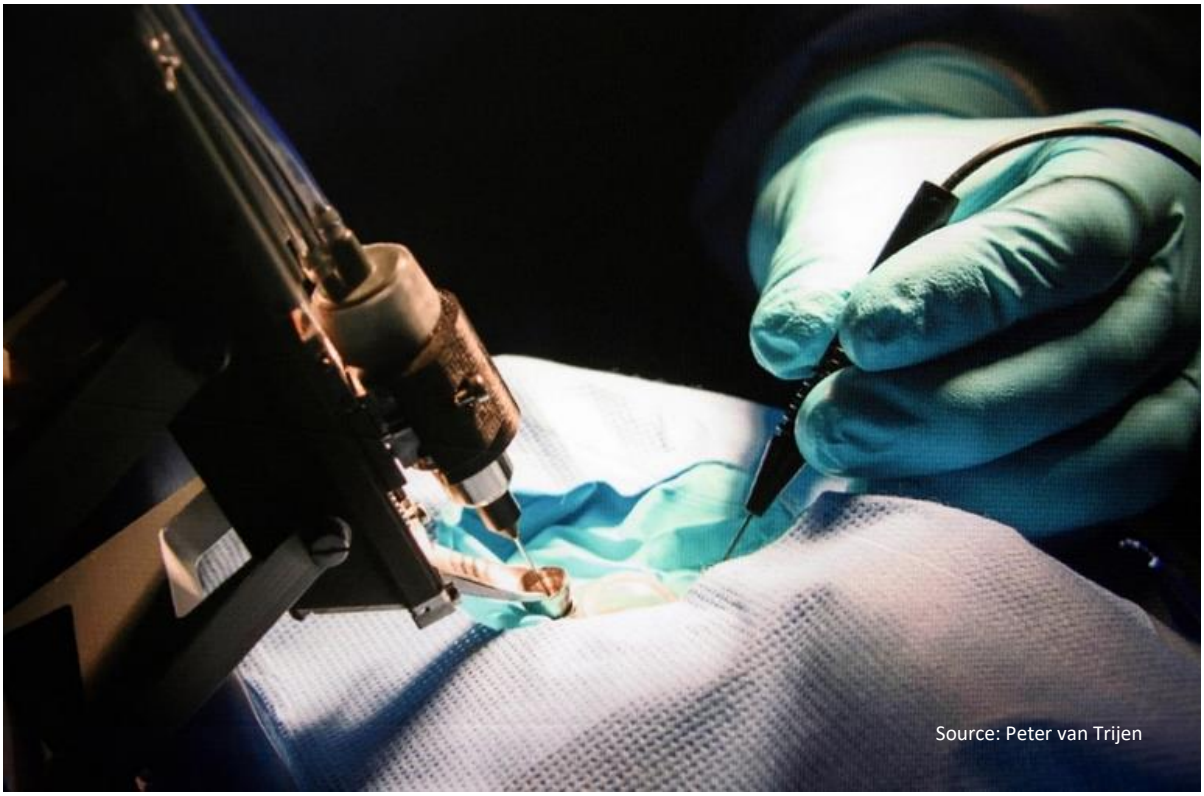
Regulatory Roadmap

Dutch medical device products to the Chinese Market





Background and Objective:

This document is coordinated by the VWS (Health, Welfare and Sport) department at the Embassy of the Kingdom of the Netherlands in Beijing. Together with the VWS-LSH & Sport China Network, the team has recognized that the knowledge and understanding of the Chinese regulatory scheme for medical products has been a challenge, for many Dutch LSH companies, especially SMEs.

This document is aimed at providing a preliminary overview of the Chinese regulatory scheme for the medical device products, in order to assist Dutch LSH companies, when tapping into the Chinese market.

The main content of this document is based on the valuable contribution of several external experts who have hands-on expertise on the Chinese market, who are listed in the 'Acknowledgement' part of the document.

Disclaimer:

This document is only intended to help relevant Dutch companies, by providing a preliminary introduction overview of the Chinese medical device product regulatory scheme. The information might not be comprehensive or accurate. It is also subject to changes in policies, both at national and at local level.

If you are seriously considering to bring your product to the Chinese market, you are recommended to hire local expertise for your specific product.

Acknowledgement:

The major contributor to this document is Ms. Stephanie Huang and her team from Qserve Group China.

Contact:

pek-vws@minbuza.nl

Nico Schiettekatte, Counselor for Health, Welfare and Sport

Sunny Liang, Senior Policy Advisor, Life Sciences and Health

Department of Health, Welfare and Sport,

Embassy of the Kingdom of the Netherlands

4 Liangmahe Nanlu, 100600 Beijing, People's Republic of China

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I Overview of regulatory roadmap to Chinese market

For a foreign medical device, the most common route to enter the Chinese market is to go through the approval process (Class II & III product), or filling process (Class I product) at the NMPA (National Medical Product Administration, former CFDA), and obtain a product certificate for the market.

Since very recently, foreign medical products can obtain domestic (made in China) certificates via a local Contract (Development and) Manufacturing Organization (CMO/CDMO). In this way, the product is recognized as a domestic product.

It is also possible to relocate the production site to China, and apply for a domestic product certificate, in addition to the foreign product certificate which has been obtained for the same scope of product. A domestic certificate may allow a foreign product to get a better penetration into the market (e.g. possible better position in public hospital procurement), under the background of made in China initiative and the Volume-based procurement (VBP).

What's more, there are also special policies of using medical products which meet certain criteria, in some special regions, prior to NMPA approval.

1 Getting an Imported Product Certificate

NMPA is the national health authority which is responsible for the regulation, approval, and supervision on the whole lifecycle of medical devices on the Chinese (mainland) market. Under the NMPA, there are about 30 provincial level MPAs. Foreign medical devices of class II & III, and domestic class III product registrations shall be approved by NMPA via a standard registration route. Foreign class I medical devices need filing with NMPA. Domestic class II devices shall be approved by province MPAs via registration, while domestic class I devices are filed with city level State Administration of Market Regulation (SAMR). Manufacturers shall submit a notarized "proof of quality qualification of the manufacturer" upon the submission. A common way for foreign manufacturers to satisfy this requirement is an ISO 13485 certificate or equivalent QMS certificate plus quality system self-inspection report, main production equipment and inspection equipment catalogue, and comparison with other products that passed an inspection. Pre-requisite for market approval in China also implies that manufacturers have prior approval in their country of origin unless their products are innovative ones.

The overall NMPA filing process may take 1-2 months, while registration process may take 12-24 months or longer. The "Center for Medical Device Evaluation (CMDE)" under NMPA performs an acceptance review on the submitted documents, and sends a review letter to the applicant in 5 working days. After the questions in the reviewer letter are answered satisfactorily, and submitted technical documents are accepted, a technical review will be performed. The first-round technical review will take sixty working days (Class II device) or ninety working days (Class III device) to issue a deficiency letter. NMPA will conduct a second-round technical review when the answers are prepared and finalize it within another sixty working days. The applicant has maximum one year to respond to all the questions listed in the deficiency letter and additional questions raised in the 2nd round review. After that, it will be the administrative review, which will take another twenty working days to process the revised result for signature, and ten working days to issue the certificate.

In addition to the technical files compiling, type testing and clinical requirements are the most time-consuming parts. The type testing timeline varies depending on the product performance and specifications. The general time frame is 3 to 6 months. The biocompatibility tests and type testing could possibly accept existing overseas reports if certain criteria are met. For new technology without published standards, or those which require special testing equipment, the type testing might take a longer time for communication and negotiation. It is recommended to have communication with test houses at an early stage, in order to select a qualified lab for innovative/complex device testing. The clinical evaluation preparation may take 1-2 months, while investigational studies (if required) may take years, depending on the risk and complexity of the

device, sites selected, Human Genetic Office approval process, regular ethics committee meeting period, subjects' recruitment, clinical follow-up, etc.

2 Getting a Domestic Product Certificate via CMO/CDMO route

A Contract Manufacturing Organization (CMO) or Contract Development & Manufacturing Organization (CDMO) provides services to certain phases in the product development. Similar to CROs (contract research organizations), CMO/CDMO is a third-party service organization which is entrusted by the manufacturer to provide R & D, design and production by contract. The role is to help a medical device manufacturer to improve their quality control, shorten the trial production timeline, reduce production costs and improve production efficiency. Such services have been available in the market for years. However, the recent implementation of the Marketing Authorization Holder (MAH) system has facilitated and boosted the emerging market for CMO/CDMO.

Before the MAH system was implemented in China, a legal manufacturer in China had to obtain both production permits and registration certificates themselves. The timeframe and financial investment needed for setting up facilities, passing and managing the quality system, and registering the device were major burdens, in particular for those start-up companies which mainly focus on product research and development.

The contracted service providers can however be specialized in setting up a quality management system, providing facility design and construction, and supporting the prototype testing and product registration.

Since March 2017, the trial program of the MAH system started from Shanghai, which allowed the manufacturers to hold the product license while contracting production or part of the development to third parties. In 2018, the pilot expanded to Guangdong and Tianjin. From August 2019 onwards, the MAH pilot program scope has been extended to 21 provinces and cities nationwide. The new pivotal Regulation on the Supervision and Administration of Medical Devices (Order 739) also further supports the MAH system from the legal regulatory perspective.

For innovative products, MAH may help to optimize the production process, verify batch production, and commercialize customized R & D to mass production.

For foreign companies, the MAH system encourages the manufacturer to set up a legal entity in China and contract manufacturing locally, in order to speed up the product launch. In this way, a foreign originated medical technology/device product can apply for a domestic certificate

3 The Special Policies/Routes

3.1 Hainan BoAo Pilot zone and Real-World Data study platform

Hainan is an island province in South China with about 10 million inhabitants. Hainan BoAo Lecheng International Medical Tourism Pilot Zone (Hope City) was established in 2013, and has been positioned as a prioritized national project in the medical field since 2019. It is also China's first platform for real-world data studies. Data collected from the clinical use of imported drugs and medical devices there could support product registration process at NMPA, which may greatly reduce the time for foreign innovative products to enter the Chinese market.

The key policy is that innovative/urgently needed pharmaceutical or medical devices, which are already approved and used in the home market (such as the U.S. and/or the European market), can be used in hospitals in the Hope City, after a light procedure at the Hainan provincial MPA. The data generated in the clinical use in Hope City, can be possibly recognized as real world data, which can support the market approval procedure by NMPA to obtain the import product certificate.

At least one medical device product from the Netherlands has been approved for use in the Hope City. The product is now in the process of applying for NMPA approval with a real world data study.

3.2 Guangdong-Hong Kong-Macao Greater Bay Area (GBA) initiative

On November 25th 2020, China State Administration for Market Regulation (SAMR) issued an action plan to promote the Development of Innovative Regulatory of Drugs and Medical Devices in the GBA of China (Circular [2020]-159) (the "Plan").

Under this plan, eligible hospitals in GBA are allowed to use imported medical products approved and used in public hospitals in Hong Kong and Macau, prior to registration with NMPA.

Geographical location: GBA include 9 mainland China cities in Guangdong province, including Guangzhou, Shenzhen, Zhuhai, Foshan, Huizhou, Dongguan, Zhongshan, Jiangmen and Zhaoqing.

Application criteria for medical devices to the GBA initiative：

1) Pilot medical institution selected by Guangdong Health Commission to submit the application to the Guangdong Medical Products Administration (GD MPA)
2) The concerned medical device product has been procured and used in public hospitals in HKG or Macao, and the product has an innovative feature, and is urgently needed in the clinical setting
3) The concerned product is on the list which is published by the GD MPA. The device products on the current list currently include: Magec Rod, Magec Manual Distractor, External Remote Controller (Magec Erc2), Spot Ex Endoscopic Tattoo, CliniMACS Plus System. This list is subject to continuous update.
4) The intended product is to be used for special medical purpose in the concerned hospital

The application procedure can be find on the website of the Gudangdong government.

3.3 Discussion

The BoAo pilot provides an option to innovative Dutch medical devices which are licensed in Europe to be used in Chinese hospitals on a small scale, before market approval by NMPA.

The process, including application, review and approval, is highly integrated as a result of the joint effort by the provincial MPA, the Health commission, and the Administration office of the Pilot Zone. The whole procedure could be very efficient, with only 7 working days.

The clinical data generated in the use of the product at the Pilot Zone hospitals, therefore could possibly be recognized as supplementary clinical evidence to support product registration with NMPA. This data can also be used as research data for publication.

The GBA initiative encourages more business activities in the region by optimizing the allocation of medical resources. As a Dutch medical device company, if your product is already used in a public hospital in Hong Kong or Macau, this initiative might be a special way for your product to enter the market of China mainland.

The medical data collected in the clinical use under this initiative could either serve the purpose of medical research, or be recognized as valid evidence to support the market registration with NMPA in the future.

Both the BoAo pilot and the GBA initiative are special regulatory routes for foreign manufacturers to consider when tapping into the Chinese market. A comparison table is listed below about the two routes.

Table 1. Comparison table between GBA route vs BoAo route

Item	GBA route	Hainan BoAo Pilot
Applicant	Designated medical institutions located in GBA originated in HK/Macau	Designated medical institutions located in BoAo
Intended product	Urgently needed for clinical use, mainly class II, and III	Innovative products / Urgently needed for clinical use, mainly class II, and III/ If similar products are already on the market, advantages of the intended product compared with the existing product should be indicated and proven
Pre-requisite	Approved and used in public hospitals in Hong Kong or Macau	Approved and used on the home market or some other countries worldwide
Application review and approval authority	GDMPA, and then jointly reviewed by GDMPA and GD Health Commission.	Submitted to BoAo MPA, and then jointly reviewed by Hainan province MPA and Hainan Health Commission.
Review and approval time	20 working days	7 working days at Hainan MPA
Device import	Be imported via GBA ports through qualified distributor for purchase, import, and distribution	Be imported from Hainan port through designated distribution channels for customs clearance or other designated customs if approved
Usage area	9 cities in GBA	BoAo Zone
Submission document	Simplified technical dossier Refer to: Application checklist for GBA initiative	Simplified technical dossier Refer to: Application checklist for BoAo program
Qualified usage time	The approval is valid for 1 year	When the clinically urgently needed imported medical devices have reached certain use quantity and use effect in medical institutions, the provincial MPA shall inform the foreign applicant to apply for import product registration with the national NMPA. If the manufacturer does not submit registration on time, the import and use of clinical products in BoAo shall be suspended After the product has obtained the registration certificate, it is no longer qualified for import as a clinically urgently needed medical device.

II. Zooming in the Practical Procedures

4 Aiming for Imported Product Certificate

4.1 Classification

Medical devices are classified into 3 categories in China—Class I, II, and III based on risk levels. Class I devices are with the lowest risk, class II devices are with moderate risk and requires moderate technical management and control, and Class III devices are those with high risk and requires strict regulatory and control. Determining a proper classification is one of the critical steps in the overall

regulatory strategy, as it leads to different registration routes, submission technical file contents, and clinical requirements.

NMPA is responsible for categorizing the classification of the medical devices, which is similar to the US FDA system. Although the NMPA published the Classification Rule (Order No.15 in 2015) to guide medical device classifications at top level, the "Medical Device Classification Catalogue" is the main reference document detailing medical devices classifications, product description, generic product name and code. Manufacturers need to select a proper classification based on the Catalogue.

If the intended device cannot be identified in the Catalogue, there are two options. One is to submit the application directly as class III device, and the other is to file the classification application to the Center for Standardized Supervision under the National Institute of Food and Drug Center (NIFDC) for further assessment.

Under the EU MDR, devices are classified into four classes: class I, IIa, IIb, and III. The actual classification of each device depends on the risk and claims made by the manufacturer for its intended use and the technology it utilizes. Manufacturers need to determine if the device is non-invasive, invasive, active, or applicable to special rules and classify it by themselves. Compared with the EU classification, the Chinese classification is more catalogue based.

4.2 If Class I

Class I devices only need to comply with the minimum regulatory requirements and are not subject to technical review by the Chinese health authority. Filing acceptance review is performed by the NMPA project management department to check the scope compliance and submission completeness on a high level. There is no application fee or annual company establishment fee applied. The class I certificate does not have a validity date either.

- Application documents: Refers to Annex I- application checklist for class I medical device.
- Application method: Postage
- Review Time: 5 working days.
- Application fee to the authority: Not applicable.

4.3 If Class II and III

- Application documents: Refers to Annex II- application checklist for class II and class III medical device.
- Application method: Electronically via ERPS
- Review Time: Filing Acceptance Review (5 working days), Technical Review 1st round (60 working days for class II, while 90 working days for class III), 2nd Technical Review after the deficiency letter issued (60 working days). Administration process after passing the technical review (20 working days) and certification (10 working days).
  The applicant has 1 year to prepare all the questions raised in the deficiency letter and submit them via ERPS.
- Application procedures include 8 steps:
  - Step 1: NDA (applicable if using external consultancy)
    A Non-Disclosure Agreement will be signed as the starting point to protect the confidential information from the client, and the device information will be gathered afterwards.
  - Step 2: Development of a regulatory strategy
    A regulatory route specific for the devices needs to be developed. It Includes:
    - Device classification
    - Selection of qualified applicable test house
    - List of requirements/documents to kick off the registration process
    - Applicable National/industry/product standards identification
    - Clinical route assessment
  - Step 3: Development of a Product Technical Requirement (PTR)
    All devices in China need a dedicated product protocol, describing the product specification, performance indicators, test methodology, and applicable national and/or industry standards

used. This will form the input for the local qualified test laboratory for performance, safety and electromagnetic compatibility testing.

- Step 4: Contract Product testing in China test laboratory and Liaison
  A qualification and availability check with NMPA accepted testing labs are required for selection. Sample devices manufactured in compliance with GMP will be required to be tested to validate its safety, performance and effectiveness. Before the test starts, the applicants need to sign the contract with the test house, submit the product technical requirements (PTR), and arrange the samples on site. The testing will focus on claimed performance and safety indicators, quality, related national/industry standards, operational environment, reliability, and sterilization etc.
- Step 5: Submission package build up
  A package of technical files in line with NMPA requirements needs to be assembled. File preparation shall follow ERPS submission checklist on Annex II- application checklist for class II and class III medical device.
- Step 6: NMPA Submission
  For Class II and Class III devices, the submission to NMPA involves both filing acceptance review and technical review. Filing acceptance review is performed by the project management department, while the technical review is performed by the technical department. The clinical part is reviewed by the clinical department. The whole process may also involve questions & answers via 2 formal written notices (major issues) and 1 informal phone call (minor issues) between the reviewer and applicants on the content of all the submitted documents.
- Step 7: Certificate issuance
  The certificate issuance takes 10 working days after the technical review and PTR approval. Certificate is issued with 5 years validity date to the legal manufacturer. The key information listed on the certificate include the manufacturer's name/address, production site address, China agent name/address, product structure, composition, and indication for use.
- Step 8: China Agent (Post Market)
  Foreign device manufacturers are required to appoint a China agent for submission and post market surveillance. Domestic manufacturers do not have such a requirement. The China agent needs to be a legal entity (a fully established company) in mainland China and shall take the required responsibilities.

- Application fee to the authority:

Classification	Registration Type	Imported Device (CNY)	Imported Device (in Approx. EUR)
Class II	Initial Registration	￥210,900.00	29845
	Change Registration	￥42,000.00	5943
	Renewal (every 5 years)	￥40,800.00	5774
Class III	Initial Registration	￥308,800.00	43700
	Change Registration	￥50,400.00	7132
	Renewal (every 5 years)	￥40,800.00	5774
	Clinical Trial Application prior to the study (only applicable for high-risk medical devices which need approval before clinical study initiation. See Appendix V)	￥43,200.00	6113

4.4 Clinical pathway

In China, there are two options to meet the clinical requirements to validate intended product's safety, performance and effectiveness as intended claims under the newly proposed clinical evaluation route in 2021. These two options are based on product features, risk levels and exiting clinical data status, and shall be reviewed/updated continuously through the entire life cycles of the devices.

- Option 1. Clinical Evaluation Exemption Route

NMPA formulates a Catalogue of Medical Devices Exempted from Clinical Evaluations. The products listed in this Catalogue may be exempted from clinical trials and may also be exempted from the clinical evaluation report (CER). When preparing the clinical document, the manufacturer needs to compare data of the intended product to the contents described in the exemption catalogue and compare data of intended product with approved predicate devices in China in terms of working principle, structure, material or the material with direct contact with human body, performance requirements, sterilization/disinfection, intended use, and use method etc. Clinical evaluation report might not be required, however, an assessment report is required to address the differences/gaps between the intended product, predicate device and device listed on catalogue if applicable.

This option is intended for low-risk products with simple documentation requirements. The low-risk products refer to devices with a clear mode of action, finalized design, and well-established technology. The equivalence devices are marketed for years without serious adverse events and without changing the standard use. Or the device's safety and effectiveness could be proved by non-clinical evaluation.

- Option 2. Clinical Evaluation Route

Under the clinical evaluation report (CER) route, there are two major ways to be in compliance. One is to demonstrate equivalence of the intended device with other approved equivalent/comparable device(s) in the market. And another is to provide the clinical investigation data of the intended device.

The equivalence option requires the applicant to evaluate the intended device through one or more predicate device(s) or comparable device(s) to compile a comprehensive clinical evaluation report. The selected predicate devices shall have already been approved in China, The predicate device needs to share the same intended use scope, same or similar technical characteristics and biological characteristics with the intended device, while the comparable device shall share the similar intended use, technical characteristics and biological characteristics broadly with sufficient scientific evidence to justify the differences. A summary document is expected to support the comparability by describing various elements listed (appendix IV) plus additional testing when needed to establish the comparability. The consideration factors in appendix replace the older requirements of comparing 16 items to make the CER compiling more feasible and scientific.

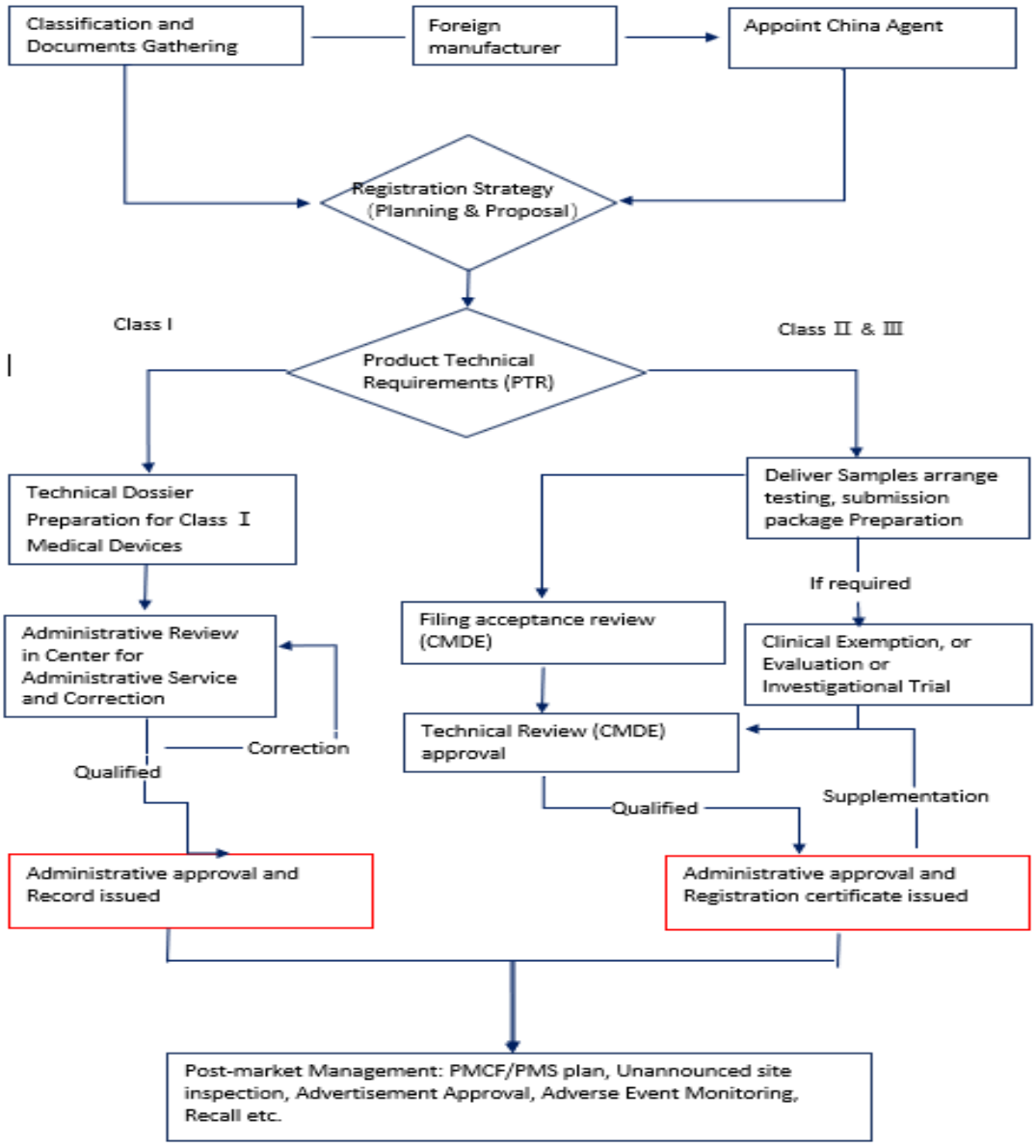
Many devices are developed or modified by incremental innovation, so they are not completely novel. Thus, it is encouraged to draw on the clinical experience data and literature reports of the safety, clinical performance and/or effectiveness of predicate/comparable devices to establish the clinical evidence. The equivalence options strongly support the existing and well-established technologies such as product intended for an established use of the technology, new generation upgrading from older one, product modification, and products sharing the same subcontracting process.

The clinical study data option is the most direct way to validate the product safety and performance. To reduce the burden of unnecessary or repeated studies, clinical investigation data is required for the high-risk products or the innovative product with little or no experience data, or high-risk product with extended clinical application out of the exiting technology, or with new material which existing clinical/non-clinical data may not be sufficient to prove its safety and effectiveness.

A clinical study shall only be arranged to generate additional data and address the unsolved concerns or new issues. Clinical trial refers to the study conducted by qualified medical institutions, in which the safety and effectiveness of a medical device are investigated. In most cases, a full set of clinical investigational study including study plan, written agreement between the sponsor and institutes, protocol, test report and EC approval shall be submitted for review. The report data can be generated either out of China or in Chinese territory, and it can be either pre-market prospectively, or post market retrospectively. Foreign data collection needs to meet conditions, such as adherence to the ethical principles set out in the Helsinki Declaration, scientifically sound study design, and compliance with country-specific requirements. The study shall be carried out in compliance with China GCP requirements or ISO14155. The applicant needs to analyze the gaps item by item for differences between China and abroad, and prove its authenticity, reliability, scientificity, and traceability.

The CER route also imposes new requirements to the writer/evaluator. It shall be composed by experienced and qualified staff and be signed and dated. A justification of the selection of clinical evaluators is deemed necessary. The evaluators shall possess the knowledge of the product and its application, grasp research methods (such as clinical trial design and biostatistics) and understand diagnosis and management of the intended diseases.

4.5 Submission procedure flowchart

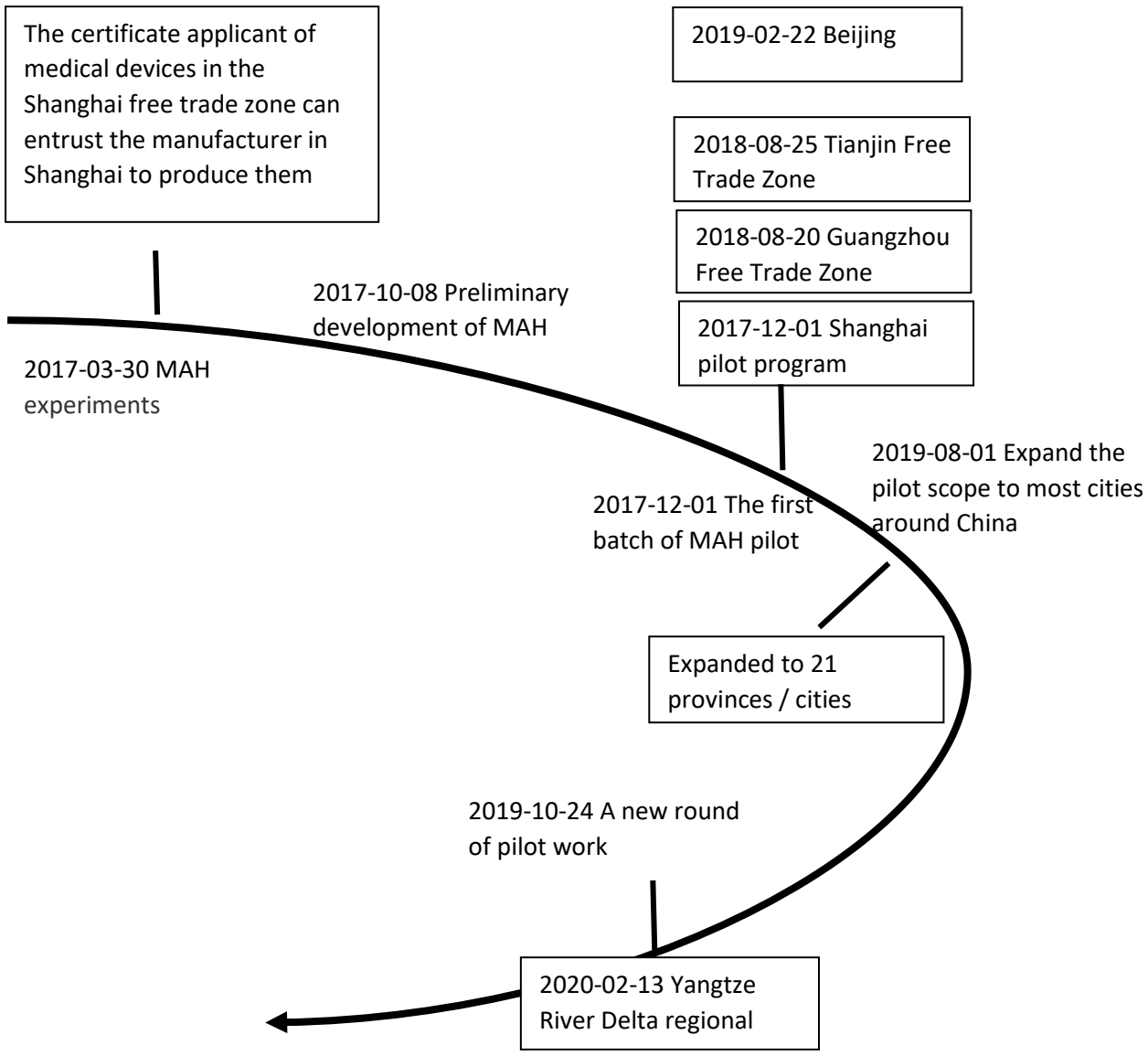


5 Aiming for domestic (Chinese)product certificate via CMO/CDMO

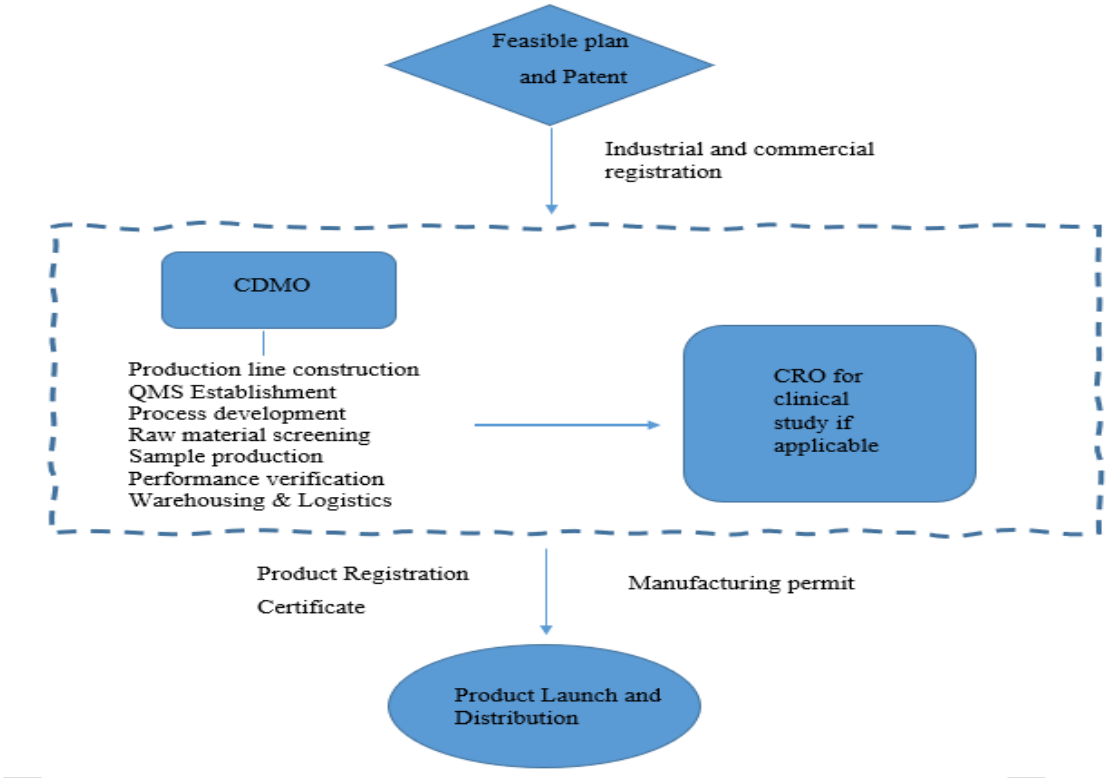
5.1 Marketing Authorization Holder (MAH) system and CMO/CDMO

The MAH system has major implications for the developers who have limited manufacturing capabilities. Companies that register devices do not have to be the manufacturers. They may commission one or multiple qualified contract manufacturing organization(s) to manufacture the approved medical devices. The device manufacturers/certificate holders may produce the products themselves or entrust one or more contract manufacturers to produce samples for registration, and mass production after the product is licensed. The certificate holder is ultimately responsible for the safety and performance of the medical device. MAH has facilitated rapid and vigorous development of CMO/CDMO service.

5.2 MAH system development flowchart



5.3 CMO/CDMO role in the registration



5.4 Cost and time

Due to the risk levels, features, and complexity of the devices, the cost and time to register a domestic product via CMO/CDMO vary. There is no suggested figure or statistical analysis publicly available on how much time could be shortened or costs could be saved via CMO/CDMO, comparing to the traditional route.

There are many CDMO service providers in China, but only a few can assist through the whole process from R&D to production of the product life cycle. Most of them are focusing on small-scale trial production or post market mass production. The manufacturer may consider the product situation to decide if/how such services are helpful.

6 About special policies/procedures

6.1 Background

In November 2020, NMPA published a draft version of Technical Guideline of Using Real-World Data (RWD) in Clinical Evaluation of Medical Devices. Real world data is becoming the important supplementary clinical evidence, in addition to the traditional trial data, in the NMPA approval process.

Foreign manufacturers can apply for a real world data program through BoAo or GBA prior to NMPA approval to close the gaps for future submission. The RWD might not be sufficiently used as independent and strong enough evidence in the evidence hierarchy model, but could be recognized by NMPA as supporting data to evaluate the risk/benefit of the device.

BoAo program for example could be a good choice for supportive bridging study to collect more treatment data on the Chinese population. As a foreign device product, if the existing clinical data on the home market is not sufficient to do a submission to China NMPA, additional study in the BoAo program can provide supporting data to do the submission via the standard route in a later phase.

By December 2021, at least two foreign devices obtained the registration certificates successfully from NMPA, with the support of the real-world studies in BoAo. They were a glaucoma drainage tube device from Allergan, which was approved in March 2020, and a Catalys Precision Laser System from AMO, which was approved in January 2021.

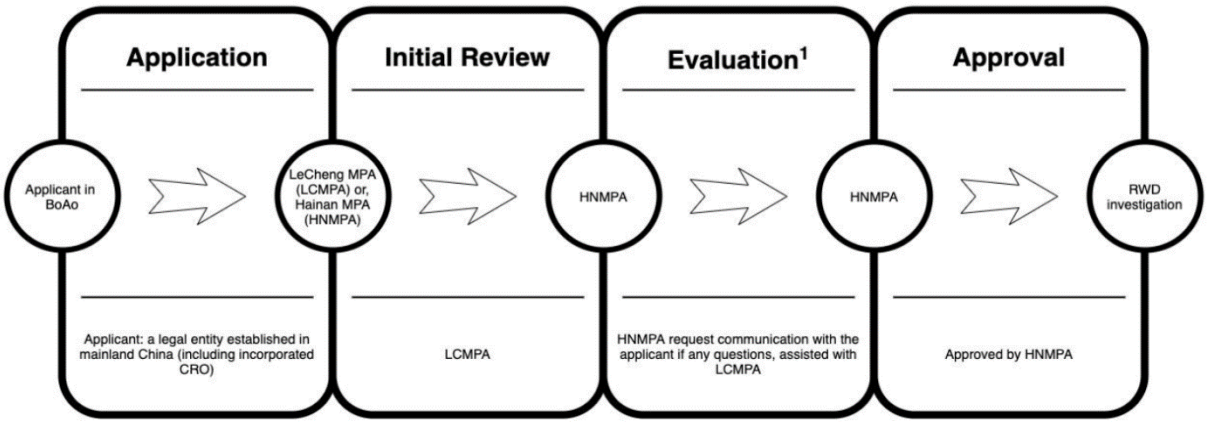
6.2 Application conditions

- New devices that have been approved in the home market or other countries in the world, but have not been marketed in China yet.
- The products could be legally imported in BoAo for clinical use upon the approval from Hainan Provincial MPA prior to NMPA pre-market certification. BoAo is currently the only real-world data platform to facilitate the study and data collection. GBA is also planning the similar platform but not fully into operation yet.
- Qualified medical institutes located in BoAo can apply and use the intended device through Real-World Data program.
- Participants can generate clinical data in the actual clinical environment in China with service fees charged.

6.3 The procedure of real-world data study program application is as follows

- Applicant submits application to local MPA. The applicant shall be a legal entity established in mainland China including a CRO or a China agent.
- The local MPA performs the initial review and evaluation. The evaluation checklist includes:
  - Evidence document (other country’s regulator’s approval out of China)
  - Primary investigator's resume and profile
  - Intended study protocol
  - Data collection and quality control plan
  - Project Plan
- Direct communication between the applicant and local MPA is usually needed
- Approval from local MPA (Hainan provincial MPA)

6.4 Real-world data study application flowchart



1. Evaluation checklist:

- evidence document (approval record out of China)
- Primary investigator's bio
- Study protocol
- Data collection and quality control plan
- Project Plan

LeCheng MPA (LCMPA) – The local MPA in BoAo region, Hainan province

Hainan MPA (HNMPA) – The local provincial level MPA, Hainan province

Appendix I: Class I Filing Checklist

#	EN	Description
1	**Class I filing form**	see 'Class I filing form - EN.docx'
2	**Risk analysis report**	The content can include for instance, identification of hazards, assessment of hazardous situation, risk reduction measures, acceptability of the remaining risk, risk management report etc.
3	**Technical Requirement**	The drafting of 'Technical Requirement' needs to follow CFDA Announcement NO.9 (2014) Guidance on Technical Requirement. This document contains mainly two aspect. 1. **Device performance indicators** - indicators relating to functionality, safety, quality control - reference to Chinese national/industry standards 2. **Test method**
4	**Test report**	Self-test report or third-party lab testing report;
5	**Clinical Evaluation**	Clinical evaluation needs to cover following: 5.1 Intended use 5.2 Use environment 5.3 Intended user 5.4 Contraindication 5.5 Comparison with same category device on the market 5.6 AE from the same category device
6	**IFU and Labeling**	Labeling sample: labeling for the smallest unit
7	**Manufacturing info**	1. Describe the manufacturing process; highlight the critical process 2. Describe the manufacturing site
8	**Certificates, License and other evidential documents**	Provide following certificates, license etc. 1.Manufacturer establishment license 2.Free sale certificate 3.Delegation letter to China agent; China agent's Commitment letter; China agent's business license (copy)
9	**Declaration of conformity**	Declaration of conformity on fulling: - Medical device filing requirement; -Class I medical device catalogue; - Product standards; Declaration of authenticity of the information provided

Appendix II: Submission checklist for class II & III

CHAPTER 1 – REGIONAL ADMINISTRATIVE	
1.01	Cover Letter
1.02	Submission Table of Contents
1.03	List of Terms/Acronyms
1.04	Application Form/Administrative Information
1.05	Listing of Device(s)
1.06	Quality Management System, Full Quality System or Other Regulatory Certificates
1.07	Free Sale Certificate/ Certificate of Marketing authorization
1.08	Expedited Review Documentation
1.09	User Fees
1.10	Pre-Submission Correspondence and Previous Regulator Interactions
1.11	Acceptance for Review Checklist
1.12	Statements/Certifications/Declarations of Conformity
1.12.01	Performance and Voluntary Standard
1.12.02	Environmental Assessment
1.12.03	Clinical Trial Certifications
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2.04	Device Description
2.04.01	Comprehensive Device Description and Principle of Operation
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2.04.03	History of Development
2.04.04	Reference and Comparison to Similar and/or Previous Generations of the Device
2.04.05	Substantial Equivalence Discussion
2.05	Indications for Use and/or Intended Use and Contraindications
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2.06	Global Market History
2.06.01	Global Market History
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3.05.01	Physical and Mechanical Characterization
3.05.01.01	[Study description, study identifier, date of initiation]
3.05.01.01.01	Summary
3.05.01.01.02	Full Report
3.05.01.01.03	Statistical Data
3.05.02	Chemical/Material Characterization
3.05.02.01	[Study description, study identifier, date of initiation]
3.05.02.01.01	Summary
3.05.02.01.02	Full Report
3.05.02.01.03	Statistical Data
3.05.03	Electrical Systems: Safety, Mechanical and Environmental Protection, and Electromagnetic Compatibility
3.05.03.01	[Study description, study identifier, date of initiation]
3.05.03.01.01	Summary
3.05.03.01.02	Full Report
3.05.03.01.03	Statistical Data
3.05.04	Radiation Safety
3.05.04.01	[Study description, study identifier, date of initiation]
3.05.04.01.01	Summary
3.05.04.01.02	Full Report
3.05.04.01.03	Statistical Data
3.05.05	Software/Firmware
3.05.05.01	Software/Firmware Description
3.05.05.02	Hazard Analysis
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3.05.05.04	Architecture Design Chart
3.05.05.05	Software Design Specification
3.05.05.06	Traceability Analysis
3.05.05.07	Software Development Environment Description
3.05.05.08	Software Verification and Validation
3.05.05.08.01	[Study description, study identifier, date of initiation]
3.05.05.08.01.01	Summary
3.05.05.08.01.02	Full Report
3.05.05.08.01.03	Statistical Data
3.05.05.09	Revision Level History
3.05.05.10	Unresolved Anomalies (Bugs or Defects)
3.05.05.11	Cybersecurity
3.05.05.12	Interoperability
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3.05.06.01	[Study description, study identifier, date of initiation]
3.05.06.01.01	Summary
3.05.06.01.02	Full Report
3.05.06.01.03	Statistical Data
3.05.07	Non-Material-Mediated Pyrogenicity
3.05.07.01	[Study description, study identifier, date of initiation]
3.05.07.01.01	Summary
3.05.07.01.02	Full Report
3.05.07.01.03	Statistical Data
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3.05.08.01	Certificates
3.05.08.02	[Study description, study identifier, date of initiation]
3.05.08.02.01	Summary
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3.05.08.02.03	Statistical Data
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3.05.09.01.01	[Study description, study identifier, date of initiation]
3.05.09.01.01.01	Summary
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3.05.09.01.01.03	Statistical Data
3.05.09.02	Manufacturer Sterilization
3.05.09.02.01	[Study description, study identifier, date of initiation]
3.05.09.02.01.01	Summary
3.05.09.02.01.02	Full Report
3.05.09.02.01.03	Statistical Data
3.05.09.03	Residual Toxicity
3.05.09.3.01	[Study description, study identifier, date of initiation]
3.05.09.3.01.01	Summary
3.05.09.3.01.02	Full Report
3.05.09.3.01.03	Statistical Data
3.05.09.4	Cleaning and Disinfection Validation
3.05.09.4.01	[Study description, study identifier, date of initiation]
3.05.09.4.01.01	Summary
3.05.09.4.01.02	Full Report
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3.05.10.01	[Study description, study identifier, date of initiation]
3.05.10.01.01	Summary
3.05.10.01.02	Full Report
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3.05.11.01	[Study description, study identifier, date of initiation]
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3.05.11.01.02	Full Report
3.05.11.01.03	Statistical Data
3.06	Non-clinical Bibliography
3.07	Expiration Period and Package Validation
3.07.01	Product Stability
3.07.01.01	[Study description, study identifier, date of initiation]
3.07.01.01.01	Summary
3.07.01.01.02	Full Report
3.07.01.01.03	Statistical Data
3.07.02	Package Validation
3.07.02.01	[Study description, study identifier, date of initiation]
3.07.02.01.01	Summary
3.07.02.01.02	Full Report
3.07.02.01.03	Statistical Data
3.08	Other non-clinical Evidence
3.08.01	[Study description, study identifier, date of initiation]
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4.02.02.01.01	Clinical Trial Summary
4.02.02.01.02	Clinical Trial Report
4.02.02.01.03	Clinical Trial Data
4.02.03	Clinical Literature Review and Other Reasonable Known Information
4.03	IRB Approved Informed Consent Forms
4.04	Investigators Sites and IRB Contact Information
4.05	Other Clinical Evidence
4.05.01	[Study description, study identifier, date of initiation]
4.05.01.01	Summary
4.05.01.02	Full Report
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6B.10	Control of monitoring and measuring devices information
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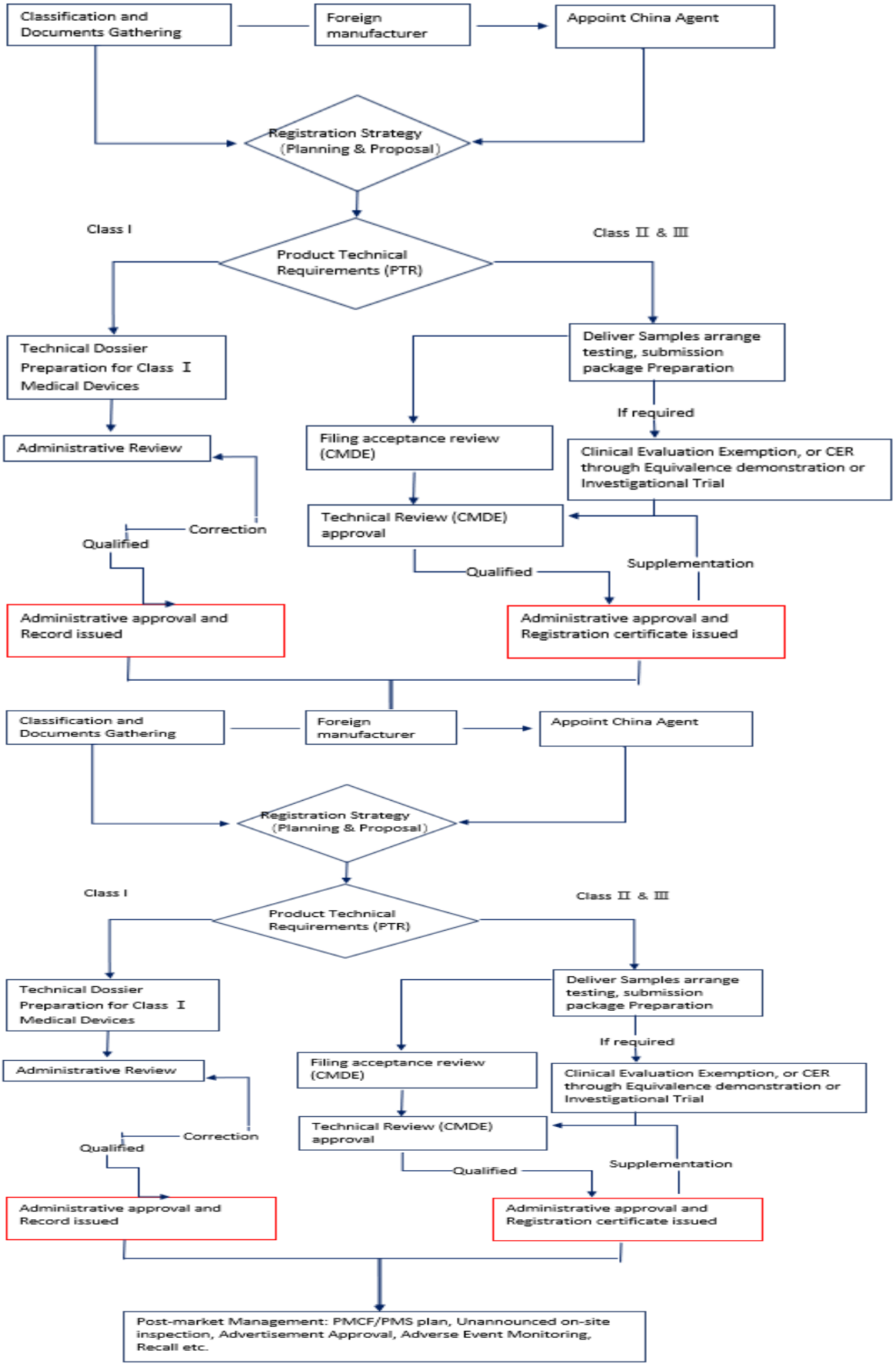
Appendix III: Flowchart of NMPA procedure



Appendix IV: Considerations for demonstrating comparability

Intended use:

- indications for use, including the disease or condition the medical device will diagnose, treat, prevent, cure or mitigate
- the severity and stage of disease
- patient population (e.g. age, gender, anatomy, physiology)
- the site of application to/in the body (organs, parts of the body, tissues or body fluids contacted by the medical device)
- type of contact (e.g. contact with mucosal membranes, invasiveness, implantation)
- duration of use or contact with the body
- environment of use (e.g. healthcare facility, home)
- intended user (e.g. use by health care professional, lay person)
- repeat applications, including any restrictions as to the number or duration of reapplications

Technical:

- design (e.g. dimensions and design tolerances; how the different components of the device system work together)
- material (e.g. chemical formulation, additives, processing such as forged, state such as crystalline)
- specifications and properties (e.g. physicochemical properties such as type and intensity of energy, wavelength, porosity, particle size, viscosity, nanotechnology, specific mass, atomic inclusions such as nitrocarburising, oxidability, tensile strength and degradation characteristics)
- deployment methods
- critical performance requirements
- principles of operation

Biological:

- degradation mechanism and profile
- biological response (e.g., inflammatory response, immune response, tissue integration)

Appendix V: Catalogue of high-risk medical devices which need approval before clinical study initiation

number	Product category	Coding number	Product description
1	Implantable cardiac defibrillator	12	Implantable pacemaker: usually composed of implantable pulse generator and torque wrench. Electrical pulses are applied to specific parts of the patient's heart through pacing electrodes. It is used to treat chronic arrhythmia. Resynchronization pacemaker can also be used in the treatment of heart failure. Implantable cardiac defibrillator: usually composed of implantable pulse generator and torque wrench. Ventricular tachycardia and fibrillation were detected and corrected by applying cardioversion / defibrillation pulses to the heart through electrodes. It is used to treat rapid ventricular arrhythmia. Resynchronization therapy defibrillators can also be used in the treatment of heart failure.
2	Implantable ventricular assist system	12	It is usually composed of implantable pump, power supply part, vascular connection and controller. It is used to provide mechanical support for blood circulation in patients with advanced refractory left heart failure, and for transitional treatment and / or long-term treatment before heart transplantation or restoration of heart function. It is used by medical institutions with heart transplantation conditions and comprehensive postoperative nursing ability. Medical staff, out of hospital nursing staff and patients must pass corresponding training. Anticoagulant therapy is forbidden in patients with intolerance.
3	Implantable drug infusion device	12	It usually consists of a drug infusion pump, a reperfusion and a catheter inlet assembly. The product is used together with intrathecal catheter for long-term drug input.
4	Artificial heart valve and endovascular stent	13	Artificial heart valve or valve repair device: generally made of polymer materials, animal tissues, metal materials and inorganic non-metallic materials, which contain or not contain surface modified substances. Used to replace or repair natural heart valves. Intravascular stent: the stent is generally made of metal (including absorbable metal materials) or polymer materials (including absorbable polymer materials), and its structure is generally grid shaped. Supports may or may not contain surface modifying substances, such as

			coatings. May contain pharmaceutical ingredients. It is used to treat atherosclerosis and various vascular diseases such as stenosis, obstruction or occlusion.
5	Tissue engineering medical products containing living cells	13/16/17	Passive implantable tissue engineering medical products containing living cells and mainly used as medical devices.
6	Absorbable internal fixation and implantation of long bones of extremities	13	It is made of absorbable polymer material or absorbable metal material, which is suitable for internal fixation of limb long bone fractures.