Medical Device Regulations in the People's Republic of China - the New Trend and the Challenges and Opportunities to European Medical Device Manufacturers

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List of Abbreviations

AIMDD	Council Directive 90 / 385 / EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices
CAPA	Corrective and Preventive Action
CFDA	China Food and Drug Administration
CMDE	Centre for Medical Device Evaluation (China)
EC	Ethics Committee
EU	European Union
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	International Electrotechnical Commission
IFU	Instructions For Use
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
MDD	Council Directive 93 / 42 / EEC of 14 June 1993 concerning medical devices
MDR	Regulation (EU) 2017 / 745 of the European Parliament and of the Council of 5 April 2017 on medical devices
MAH	Marketing Approval Holder
NMPA	National Medical Products Administration (China)
PTR	Product Technical Requirement
QMS	Quality Management System
SAMR	State Administration for Market Regulation (China)
SFDA	State Food and Drug Administration (China)
UK	United Kingdom

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1. Background

With its large population, the People's Republic of China (will be abbreviated as “China” in the rest of this thesis) is not an ignorable market to most foreign medical device manufacturers, many of which are based in the EU. However, having a marketing approval in the EU does not guarantee a marketing approval in China. To many European manufacturers, the Chinese medical device regulations are complex, challenging and ever-changing.

In March 2013 the former State Food and Drug Administration (SFDA) has been reconstructed into the China Food and Drug Administration (CFDA), subsequently the Chinese medical device regulations went through many changes and the CFDA attempted to better normalize the review and approval procedures for medical device applications. Since the new version of the "Regulations for the Supervision and Administration of Medical Devices" [1] and the "Provisions for Medical Device Registration" [2] came into force in 2014, more new regulations and guidelines have been issued in China, providing clarifications to critical issues such as the requirement on clinical evaluations. Meanwhile, China actively participated in international exchanges of medical device regulations. In 2013 China has become a full member of the IMDRF [3] and in 2017 China has become a regular member of the ICH [4]. As the approaches to reform the medical device approval system in China, the CFDA issued the “Special Review Procedure of Innovative Medical Devices (interim version)” in 2014 [5] and in January 2018 finalized the “Guideline on Accepting Foreign Clinical Data” within just 3 months after the draft being published [6] [7]. Compared to the previously medical device approval system that mainly based on local test data, such approaches indicated positive signs that China is being more open to new medical technologies. Additionally, many significant changes have been proposed in the "Regulations for the Supervision and Administration of Medical Devices (draft version)" [8] that have been submitted to the state council in November 2017, the proposals are currently under discussion.

In March 2018 the CFDA has been reconstructed into the National Medical Products Administration (NMPA), which is now under the supervision of the State Administration for Market Regulation (SAMR). New changes to the medical devices regulations in China are to be expected. In August 2018 the

SAMR issued the “Provisions for Adverse Events Surveillance and Re-assessment of Medical Devices” [9]. The post market surveillance of medical devices in China will be strengthened. In November 2018 the NMPA revised and finalized the “Special Review Procedure of Innovative Medical Devices” [10]. The qualification of innovative devices has been further clarified and the review procedure will be normalized.

1.1 Aims and objectives

The aim of this thesis is to provide a general but systematic review of the current medical device regulations in China and analyse the gap between the regulatory requirements in China and in the EU, with the focus on application procedures for imported medical devices in China and the consideration of possible challenges to be faced by European medical device manufacturers that comply already with the medical devices regulations in the EU.

This thesis will also analyse the new trend in Chinese medical device regulations and discuss the possible opportunities and challenges to be brought to European medical device manufacturers.

1.2 Notes

Considering that many regulations (e.g., the classification system and technical documentation requirements) of in vitro diagnostic devices are significantly different from those of medical devices both in China and in the EU, this thesis will not cover in vitro diagnostic devices.

Most of the Chinese regulations have been published in Chinese only. Some of the articles and requirements quoted in this thesis have been translated from the original Chinese texts into English by the author of this thesis. Notes will be added when the quoted texts are translated from the original Chinese texts.

2. Marketing Approval System for Medical Devices in China

According to Article 2 and Article 5 of the “Provisions for Medical Device Registration”, all medical devices sold and used in China shall apply for registration or filing. Class I medical devices shall apply for filing (refer to chapter 3.3); class II and class III medical devices shall apply for registration (refer to chapter 3.2). For imported medical devices, the applications should be submitted to the NMPA. A foreign applicant shall appoint an agent in China to conduct the communication with the NMPA and activities defined by corresponding regulations. According to Article 12 of the same “Provisions”, the language of submission dossiers should be Chinese; regarding original documents of foreign languages, both the original copy and translated Chinese copy should be submitted.

2.1 Qualification of the applicant

As regulated by Article 6 and Article 9 of the “Provisions for Medical Device Registration”, the registration applicant or filing entity brings the products to the market in his own name and shall establish and maintain the quality management system that covers the design and manufacture of the products to be approved or filed in China. This requirement basically restricted the registration applicant / filing entity to the “manufacturer” as defined by the MDD and the MDR.

2.2 “Agent” of Imported Medical Devices

In China, the role of “Agent” of imported medical devices is similar to the role of “Authorised Representative” in the EU. Both shall be responsible for the communication between the manufacturer and the authority, and for post market surveillance activities according to the corresponding regulations. The name and address of the agent shall appear on the Chinese label and in the Chinese IFU of imported medical devices in China, while the name and address of the authorised representative shall appear on the label and in the IFU of medical devices to be marketed in the EU.

Neither the MDD nor the AIMDD include detailed description of the role and obligations of an authorised representative, giving the flexibility to define the

detailed responsibilities in the contract between the manufacturer and the authorised representative. However more detailed requirements have been included in the MDR. In China, even though the "Provisions for Medical Device Registration" has already defined certain obligations of an agent, the NMPA published a draft version of the "Provisions for the Supervision and Administration of Agents of Imported Medical Devices" [11] in August 2018, giving more detailed definition of the role and obligations of an agent. According to this draft, the agent of imported medical devices shall have the following obligations (note: translated into English by the author of this master thesis):

- Apply for filing and registration according to corresponding regulations;
- Monitor and report adverse events from devices sold in China; cooperate in event investigations;
- Conduct product recalls and report to authorities;
- Assist the authorities in investigating violations of Chinese regulations by foreign "Marketing Approval Holders" (MAHs); (note: new requirement)
- Cooperate in product sampling and evaluation of product quality and provide information and data as requested by the authorities; (note: new requirement)
- Maintain the traceability of devices sold in China and keep the information of domestic marketing and distributions; (note: new requirement)
- Communicate with authorities and foreign MAHs and inform the latter about relevant regulations and technical requirements (also amended ones) in timely manner;
- Assist foreign MAHs in completing the remaining tasks from conditional approvals[1]; (note: new requirement)
- Take care of domestic complaints and inform foreign MAHs about related information; (note: new requirement)
- Undertake joint responsibility for product quality and violation of regulations.

[1] Translated into "conditional approvals" by the author, because such certificates regularly contain the wording "approved based on the following conditions …".

2.3 Classification of Medical Devices

As defined by *Table 1* and *Table 2* below from the "Rules for Classification of Medical Devices" [12] issued by the CFDA in 2015, medical devices are classified into class I, II and III based on their risk levels.

Body-contacting device												
Non-active device	Status of use / Patterns of use		Temporary use (< 24 h)			Short-term use (≥ 24 h; < 30 day)			Long-term use (≥ 30 day)		
			Skin / Orifice (openings)	Trauma / Tissue	Blood circulation / Central nerve	Skin / Orifice (openings)	Trauma / Tissue	Blood circulation / Central nerve	Skin / Orifice (openings)	Trauma / Tissue	Blood circulation / Central nerve
	1	Liquid transportation device	II	II	III	II	II	III	II	III	III
	2	Blood and other body fluids alternation device	–	–	III	–	–	III	–	–	III
	3	Medical dressing	I	II	II	I	II	II	–	III	III
	4	Invasive device	I	II	III	II	II	III	–	–	–
	5	Reusable surgical device	I	I	II	–	–	–	–	–	–
	6	Implantable device	–	–	–	–	–	–	III	III	III
	7	Contraceptive and family planning device (excluding reusable surgical device)	II	II	III	II	III	III	III	III	III
	8	Other non-active devices	I	II	III	II	II	III	II	III	III
Active Device	Status of use / Patterns of use		Minor injury			Moderate injury			Serious injury		
	1	Energy treatment device	II			II			III		
	2	Diagnostic and monitoring device	II			II			III		
	3	Liquid transportation device	II			II			III		
	4	Ionizing radiation device	II			II			III		
	5	Implantable device	III			III			III		
	6	Other active devices	II			II			III		

Notes: 1. "I", "II" and "III" herein respectively refer to class I, II and III medical devices.

2. "-" herein means the situation is inapplicable to any class of medical devices.

Table 1: Medical Device Classification (Body-contacting devices)

Non-body-contacting device					
Non-active device	Status of use / Patterns of use		little impact	Minor impact	Significant impact
	1	Nursing device	I	II	–
	2	Device for medical device sterilization and cleaning	–	II	III
	3	Other non-active devices	I	II	III
Active device	Status of use / Patterns of use		little impact	Minor impact	Significant impact
	1	Clinical laboratory instruments	I	II	III
	2	Stand-alone software	–	II	III
	3	Instruments for medical devices disinfection and sterilization	–	II	III
	4	Other active devices	I	II	III

Notes: 1. "I", "II" and "III" herein respectively refer to class I, II and III medical devices.

2. "-" herein means the situation is inapplicable to any class of medical devices.

Table 2: Medical Device Classification (Non-body-contacting devices)

However while in the EU medical devices are to be classified based on certain general rules set out in Annex IX of the MDD or Annex VIII of the MDR, in China the classification of a medical device has to be made in accordance with the "Medical Device Classification Catalogue" [13] and a product code shall be assigned to each medical device accordingly. The above-mentioned catalogue will be updated from time to time and the current version has been issued in 2017 by the CFDA. Compared to the previous version, this new catalogue has expanded from 22 sub-catalogues to 43 sub-catalogues and examples have been increased from 1008 to 6609, with the addition of indication and description for each medical device and the reclassification of medical devices from 40 categories into the lower class. [14]

Finding the correct product code not only determines the product classification but also helps identifying the applicable Chinese standards correctly. In case there is no applicable category for the device to be classified, the applicant can apply for the correct classification or submit directly to the NMPA as a class III device (the NMPA will determine the correct classification during the technical review).

2.4 Registration Units

It is very common that manufacturers combine different medical devices or components for the clinical application as systems or procedure packs.

According to Article 12 of the MDD and Article 22 of the MDR, no extra CE marking will be needed for systems or procedure packs if the requirements have been met. This actually gives the flexibility in choosing different CE marking approaches for the combination of medical devices or components, either treating the combination as a device in its own right or applying for conformity assessment for each component included individually.

In China, the applicant has less flexibility in defining a registration unit. In 2017 CFDA issued the "Guideline on Division of Registration Unit" [15], providing clarifications on the criteria for dividing different products and components into separated applications. Incorrect defined registration unit could result in the submission being rejected. According to the above-mentioned guideline, the following rules should be considered (note: translated into English by the author of this master thesis):

a) Active devices

- Devices of different technical principle should be submitted separately;
- Devices of different structure / component that affects product safety and efficacy should be submitted separately;
- Devices of different performance criteria that leads to different application scope or mechanism should be submitted separately;
- Devices of substantially different application scope should be submitted separately;
- Active devices and the non-active consumables that have to be used together should be submitted separately;
- Independent active devices to be used together in the same application scope should be submitted separately;
- The main console and its applied parts should be submitted in the same submission;
- Accessories with different intended use should be submitted separately;

- Active accessories and non-active accessories that are regulated as medical devices should be submitted separately unless they are packed in the same sterile packaging.

b) Non-active devices

- Devices of different technical principles should be submitted separately;
- Devices with and without drug / active ingredients should be submitted separately;
- Devices of different surface treatments or structures that affect the safety and efficacy should be submitted separately;
- Devices of different physical appearances that affect the safety and efficacy should be submitted separately;
- Non-active devices and its active accessories should be submitted separately;
- Devices of different structures/components or processed by different procedures that affect the safety and efficacy should be submitted separately;
- Single use and reusable devices should be submitted separately if the difference affects the performance criteria;
- Devices treated by different sterilization processes should be submitted separately if the difference affects the performance criteria;
- Devices of different structure that leads to different performance criteria or different application scope should be submitted separately;
- Devices to be used in combination with different products that affects the performance criteria should be submitted separately;
- Devices of different animal origins should be submitted separately;
- Devices of different application scopes should be submitted separately.

2.5 Marketing Approval Certificates

The registration certificates issued by the NMPA to class II and class III imported medical devices are valid for 5 years and should have the information listed below: [16] (note: translated into English by the author of this master thesis)

- Certificate No.
- Name of the applicant

- Registered address of the applicant
- Address of the manufacturing site
- Name of the agent
- Registered address of the agent
- Product name
- Models and specifications
- Structure and components
- Application scope
- Attachment: Product Technical Requirement (PTR)
- Notes (in case of conditional approval)
- Issue date and expiry date

According to Article 49 of the “Provisions for Medical Device Registration”, approval is requested for any change to the content on this certificate and its attachment(s). Special attention should be paid to the attached PTR, which will include technical specifications, testing criteria and testing methods of the approved medical device. For each change in the PTR, even not being the major change, a change application should be submitted. The importance of PTR will also be discussed in later chapters of this thesis.

A change approval is a supplement to the initial certificate and is valid until the expiry date of the initial certificate. It should have the information listed below: [16] (note: translated into English by the author of this master thesis)

- Certificate No. (of initial certificate)
- Product name
- Change description (before and after change)
- Notes: this document is to be used with “xxxx” certificate
- Approval date

For class I medical devices, only an acceptance notice of the filing will be issued, which has no expiry date. [16]

2.6 Label and IFU

As regulated by the “Provisions for Instructions and Labels of Medical Devices” [17] issued by the CFDA in 2014, the medical devices being sold and

used in China should be accompanied by the Chinese label and IFU. However, the Chinese label and IFU should not be a simple translation of the label and IFU used in the EU. Additional information has been requested by the provisions mentioned above, in particular the following:

Additional information	Chinese label	Chinese IFU
Manufacturing site address (if applicable, the name and address of contract manufacturer)	x	x
Name, address and contact information of the agent	x	x
Registration certificate number or filing number	x	x
PTR number		x
Manufacturing date, shelf life or expiry date	x	x*
**Note: this is a mandatory section of the Chinese IFU; wordings like "please refer to the label" should be included when it's not practical to include the manufacturing date / expiry date in the IFU.*		

Table 3: Additional information in Chinese label and IFU

3. Application Procedures for Marketing Approvals of Imported Medical Devices in China

3.1 Application Types

For class I medical devices, filings should be submitted for initial record or for changes of a filed record. No technical review will be involved. [2]

For class II and class III medical devices to be marketed in China for the first time, initial registration application should be submitted, and the approval will be issued after the technical review for initial registration. For changes of administrative information on the registration certificate or its attachments, a filing should be submitted, and no technical review will be involved; for changes to other approved items on the registration certificate or its attachments, a change application should be submitted, and the approval will be issued after the technical review for change application.

A renewal application should be submitted at least 6 months before the expiry date of the certificate and the approval will be issued after the technical review for renewal application. [2]

For changes to approved IFUs of class II and class III medical devices, filings should be submitted according to a specific IFU change procedure. A rejection notice will be issued if the change should involve technical review, in which case a change application should be submitted instead. If no rejection notice has been issued within 20 working days after the acceptance date, then the proposed IFU changes can be implemented. [18]

For imported medical devices, all the above-mentioned filings or applications should be submitted to the NMPA. [2]

3.2 Application procedures for approval of class II and class III imported medical devices

The CMDE website listed the following procedures that the applicant has to take into consideration during the preparation of the application, the technical review by the CMDE and the post market phase for class II and class III imported devices. [19]

	Mandatory procedure	**Optional procedure**
Preparation phase		Pre-application consulting
		Classification application
	Type testing	
	Clinical evaluation	
		Innovation qualification
Technical review phase	Acceptance of application	
		Priority qualification
	Supplement request	
		Expert meeting
		Rejection / Withdrawal
	Approval	
Post market phase		Change application
	Renewal application	
		IFU change application

Table 4: Application Procedures

Type testing and clinical evaluation are both categorized as mandatory procedure for applications in China, while in the EU type testing is not mandatory but depends on which conformity assessment route the manufacturer selects. The detailed requirements on type testing and clinical evaluation will be discussed in chapter 4 of this thesis.

3.2.1 Approval procedures (flowchart)

According to the guidelines issued by the CFDA in 2017 on the initial registration, the change application and the renewal application for class II and class III imported medical devices [20] [21] [22], the processes are similar and can be summarized into the flowchart from *Figure 1* below:

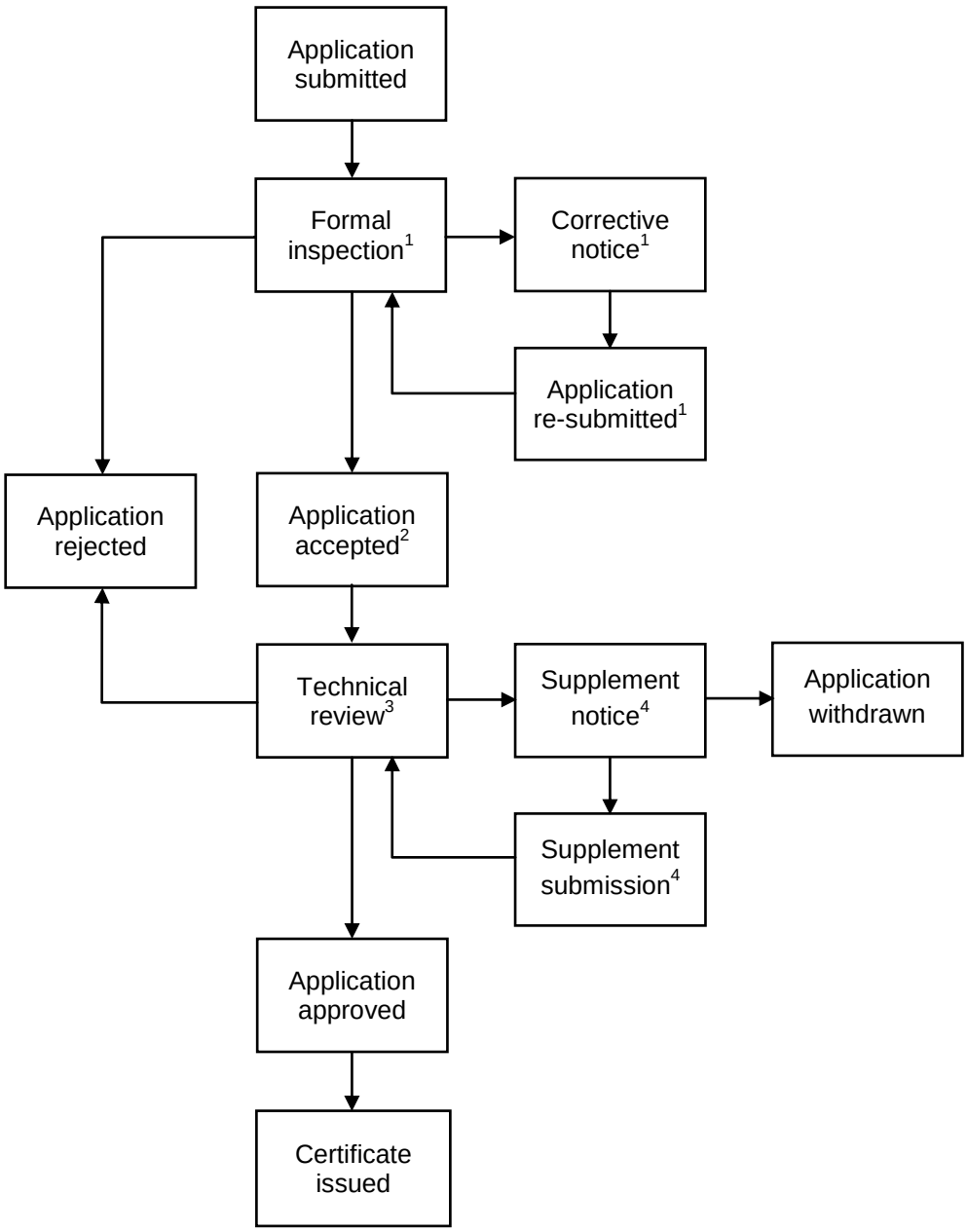

Figure 1: Marketing approval procedure

Notes:

1. Formal inspection to be conducted by the administrative service centre of the NMPA;
2. Decision of acceptance to be made by the administrative service centre of the NMPA;
3. Technical review to be conducted by the CMDE;
4. Only 1 chance of supplement submission (must be submitted within 1 year); only 3 face-to-face discussions with the reviewer will be allowed; only 1 chance of pre-review before the supplement submission will be allowed.

3.2.2 Application timeline

The timelines for initial registration, change application and renewal application in China can be summarized into *Table 5* below:

Procedure	**Timeline**
Formal inspection	5 working days
Transfer of documentation	3 working days
Technical review	Class II: 60 working days Class III: 90 working days
Decision of approval	20 working days (+ 10 working days if necessary)
Issue of certificate	5 working days
Notes: 1. Clock stops on the issue date of supplement notice and re-starts on the reception date of supplement submission 2. The above listed timeline does not include extra time for expert meetings and / or on-site audit	

Table 5: Application timeline

3.2.3 Application requirements

3.2.3.1 Initial registration of imported medical devices

For class II and class III imported medical devices to be marketed in China for the first time, a dossier including the following sections listed in *Table 6* below should be submitted for initial registration applications according to the "Guideline on Initial Registration of Imported Medical Devices" issued by the NMPA in 2018.

First level title	Second level title
1. Application form	
2. Qualification files	
3. Basic requirement list for the safety and efficacy	
4. Summary info	4.1 Overview 4.2 Product description 4.3 Models and specifications 4.4 Packaging description 4.5 Intended use and contraindications 4.6 Equivalent product or product of previous generation (if applicable) 4.7 Others
5. Research data	5.1 Performance 5.2 Biocompatibility 5.3 Biological safety

	5.4 Disinfection and sterilization process 5.5 Shelf life and packaging 5.6 Animal studies 5.7 Software 5.8 Others
6. Manufacturing info	6.1 Manufacturing process of non-active / active devices 6.2 Manufacturing sites
7. Clinical evaluation	
8. Product risk assessment	
9. Product technical requirement	
10. Registration test report	10.1 Test report 10.2 Pre-evaluation conclusion
11. IFU and labels	11.1 IFU 11.2 Label samples of units for sale
12. Declaration of conformity	
Note: translated into English by the author of this master thesis.	

Table 6: Documentation for initial registration

3.2.3.2 Change application

As regulated by Article 49 of the “Provisions for Medical Device Registration”, in China, applications should be submitted for all changes to the initial registration certificate and related attachments. For changes to administrative information, a filing should be submitted; for other changes, a change application for approval should be submitted.

According to the “Guideline on Change Application of Imported Medical Devices” issued by the NMPA in 2018, a dossier including the following sections listed in *Table 7* below should be submitted for change applications of class II and class III imported medical devices.

Section	Notes
1. Application form	
2. Qualification files	
3. Declaration on changes	
4. Copy of initial approval certificate and previous change approvals	
5. Descriptions of changes	Change comparison form and explanations

	on the following items, if applicable: - product name; - product technical requirement; - model and specifications; - structure and components; - intended use; - on manufacturing site address; - on other content in the certificate; - on other changes
6. Risk management report regarding the changes	
7. Evaluation on changes to the safety and efficacy	*Clinical evaluation is a must for changes to intended use.
8. Registration test report regarding changes to the PTR	
9. Declaration of conformity	- Conformity to Chinese regulations and standards, with a list of applicable Chinese standards; - Self-declaration on truthfulness
Note: translated into English by the author of this master thesis.	

Table 7: Documentation for change application

3.2.3.3 Renewal application

According to the "Guideline on Renewal Application of Imported Medical Devices" [22] issued by the NMPA in 2018, a dossier including the following sections listed in *Table 8* below should be submitted for the renewal of existing marketing approval of class II and class III imported medical devices.

Section	Notes
1. Application form	
2. Qualification files	
3. Declaration on no change	*no change to the most recent approval (initial or change approval)
4. Copy of initial approval certificate and previous change approvals	
5. Summary and related documentation on the remaining tasks required by conditional approval.	*the previously requested summary report on post marketing surveillance has been exempt in the 2018 revision issued by NMPA [18]
Note: translated into English by the author of this master thesis.	

Table 8: Documentation for renewal application

Since the issue of the “Provisions for Medical Device Registration” in 2014, the CFDA offered to simplify the procedure of renewal application and accelerate the technical review. To achieve such simplification and acceleration, the renewal application has been restricted to the “non-change renewal application” and has to be submitted separately from change applications [16] [22]. The previous approach of combining the renewal and change applications together are no longer allowed. In 2018 the NMPA revised again the documentation requirement for renewal applications [27], further simplifying the documentation for renewal submissions. This is to align with the new “Provisions for Adverse Events Surveillance and Re-assessment of Medical Devices”, which requires the MAH to submit periodically a summary of adverse events, surveillance data, risk assessment and management to the responsible authorities.

Although the documentation for renewal submission has been simplified, it doesn’t mean technical review will be omitted. According to Article 55 of the “Provisions for Medical Device Registration”, the renewal application shall not be approved if the most recent version of applicable Chinese standards cannot be met or the tasks listed on the initial registration certificate have not been completed. Hence it is still possible that additional tests and data being requested to get the initial certificate renewed. The applicant should review the up-to-date status of the Chinese standards being referred to and identify if any new Chinese standards not being referred to could be applicable as well.

3.3 Filing of class I imported medical devices

The filing of class I imported medical devices should be submitted to the NMPA. The administrative service centre of the NMPA will check the format and completeness of the filing dossier. If it complies with the required format, a notification on acceptation of the filing dossier will be issued upon reception.

According to Article 9 of the current “Regulations for the Supervision and Administration of Medical Devices”, the following documentation should be submitted for the filing of class I medical devices (note: translated into English by the author of this master thesis):

- risk assessment documentation;

- product technical requirement;
- product test report;
- clinical evaluation documentation;
- product IFU and label sample;
- quality system documentation related to product development and manufacture;
- other data to demonstrate the product safety and efficacy.

4. Discussion

4.1 Possible challenges from the current medical device regulations in China

4.1.1 The importance of "Agent"

Chapter 2.2 introduced the role of "Agent" in China and its obligations. To further discuss the similarity and differences between the role of "Agent" in China and the role of "Authorised Representative" in the EU, *Table 9* below summarizes the major obligations of these two roles as defined by corresponding regulations. It is worth noting that both in China and in the EU the trend is to better supervise the local agent / representative.

	Agent in China		**Authorised Representative in the EU**	
Role and obligations	Current provisions	Planned provision (draft)	MDD / AIMDD	MDR
The sole representative		x		x
Communication between the authority and the manufacturer	x	xx	x	xx
Establish a quality management system	x	xx		
Submit the application for filing or registration	x	x		
Provide to the authority the evidences of regulatory compliance	x	x	x	xx
Post market surveillance and vigilance activities	x	xx	x	xx
Note: x = covered; xx = strengthened				

Table 9: Comparison between "agent" and "authorised representative"

The contract between the agent and the foreign applicant is not the subject of review by the NMPA. It is the responsibility of both the applicant and the agent to make sure that the contract covers the requested obligations completely. In each application the agent shall submit to the NMPA a declaration on fulfilling all the obligations defined by regulations in China.

4.1.2 Possible classification differences

The medical device classification rules in China have been explained in chapter 2.3. The most significant difference between the classification rules is that in China the intended duration of use has been divided into “temporary” (< 24 h), “short-term” (≥ 24 h; < 30 day) and “long-term” (≥ 30 day), while both the MDD and MDR divide the duration into “transient” (< 60 min), “short-term” (≥ 60 min; ≤ 30 day) and “long-term” (> 30 day). Due to this difference, the “short-term” devices in the EU that claim to be used for at least 60 minutes but less than 24 hours will be defined as “temporary” devices in China and possibly classified into a lower class than in the EU.

Certain special rules from the same classification rules mentioned above will also cause discrepancies, such as:

- A medical device supplied in sterile state shall always be classified as class II or above;
- A medical device with measuring function shall always be classified as class II or above.

Because technical review by the CMDE is mandatory for class II and class III imported medical devices, if a class I device in the EU has been classified into higher class in China, it is possible that the CMDE will review extra data and information that have never been requested by the notified bodies.

4.1.3 Possible difference in registration unit

According to the rules described in chapter 2.4 for defining a registration unit for medical device submissions in China, it is possible that the compilation of a system / procedure pack (the registration unit) in China has to be defined differently from the approved system / procedure pack in the EU. According to Article 12 of the MDD, the entity that puts the system / procedure pack on the European market does not have to be the “manufacturer” of the system / procedure pack. However as explained already in chapter 2.1, in China the registration applicant or filing entity has to be the manufacturer of the registration unit. Hence it will cause issues if the applicant does not have the quality management system that covers the design and manufacture of the whole system / procedure pack (registration unit) to be approved or filed in China.

4.1.4 Possible issues with the Chinese label and IFU

Chapter 2.6 summarized the additional requirements on the Chinese label and IFU. It is worth noting that according to section 13.1 in Annex I of the MDD and section 23.1 (d) in Chapter III of the MDR, instructions for use shall not be required for class I and class IIa devices if such devices can be used safely without any such instructions. However, in China, no such exemption has been included in the provisions mentioned above.

It is also worth noting that although the Chinese label and IFU of medical devices are also subject to review by the NMPA, they are not issued as attachments of the approval certificate for medical devices. According to Article 49 of the “Provisions for Medical Device Registration”, only changes to the certificate and related attachments are subject of review and approval by the NMPA. For changes to the approved Chinese IFU of class II and class III devices, according to the “Filing Procedure of Changes to Medical Device IFUs” [18] published in 2015, a filling should be submitted to the NMPA, as explained in chapter 3.1.

4.1.5 Triggers for an “initial registration”

Chapter 3.2.3.1 deals with the documentation to be submitted for an “initially registration” of class II and class III medical devices in China. Such an “initial registration” literally applies to any device that has never been marketed in China before. However, based on the experiences from the author of this thesis, the NMPA may request the applicant to submit an “initial registration” if the proposed changes of the approved medical device are considered by the NMPA as significant. Additionally, if the renewal application for the existing certificate has not been submitted and accepted by the NMPA within the regulated deadline, an “initial registration” shall be submitted instead.

Chapter 4.1.6.2 will further discuss when a change application could trigger an initial registration submission.

4.1.6 Possible issues with the submission dossier

4.1.6.1 Initial registration

The general structure and requirements of the initial registration submission dossier of class II and class III medical devices in China share a lot of

common features with the GHTF document “Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)” [23]. Considering that the technical documentation in accordance with the MDD or the MDR also shares a lot of common features with the STED, the existing data generated for the technical documentation for CE approval should be able to cover a major part of the submission dossier for initial applications in China.

Special attention should be paid to the following sections, which would require additional data in comparison to the technical documentation of a CE marked device or otherwise cause discrepancies:

A) Product Technical Requirement (PTR)

As requested by Article 15 of the “Provisions for Medical Device Registration”, for class II and class III medical devices, the PTR should be submitted for approval, and the devices being marketed in China should comply with the approved PTR.

According to the “Guideline on drafting Product Technical Requirement” [24] issued by the CFDA, the PTR should include the following content: (note: translated into English by the author of this master thesis)

1) Product name;
2) Product models / specifications and descriptions of all the differences between them;
3) Performance criteria related to the function, safety and quality control of the finished product; the criteria should at least meet the requirements from applicable mandatory Chinese national and industrial standards.
4) Testing method to verify that the finished product can meet the criteria.

The PTR is a China specific document. It includes crucial information from product design as well as necessary quality control measures. It is crucial for medical device approvals in China not only as an important attachment to the registration certificate that defines the product models / specifications and performance criteria, but also as

the link between the product design, quality control and Chinese standards.

It is worth noting that the Chinese standards will be updated periodically, and the PTR should always take reference to the latest version of Chinese standards. It is actually similar to the reference of latest harmonized standards in the technical documentation for CE approval. Although many Chinese standards are actually adopted from harmonized standards such as ISO and IEC standards, discrepancies and different interpretations do exist. It is also very common that the most recent Chinese standard is adopted from an obsolete version of the equivalent harmonized standard because the adoption will take time. Hence when referring to Chinese standards in the PTR, it is necessary to evaluate the possible discrepancies between the requirements in China and in the EU.

B) Registration test report

Chinese test institutions conduct type testing for different purposes. Type testing for registration purpose is conducted in accordance with the PTR proposed by the applicant and reviewed by the test institution. It has to be a full test with test samples manufactured in the controlled quality management system.

In the EU, type testing is not always necessary to get market approvals depending on the conformity assessment route selected by the manufacturer. However, in China, the registration test report issued by a qualified Chinese test institution is mandatory and the pre-evaluation conclusion from the same test institution has to be submitted as well for initial applications according to the current “Provisions for Medical Device Registration”.

C) Clinical evaluation, clinical trial

According to Article 22 of the current “Provisions for Medical Device Registration”, clinical trial has to be conducted for all class II and class III medical devices, unless the product is on the exemption list or it applies one of the following criteria:

1) Where the functional mechanism of the device is definite, the design is finalized, the production process is well-established, and an equivalent marketed medical device has been in clinical use for years and no serious adverse events are recorded, and its conventional purposes of use are not changed;
2) Where safety and effectiveness of the device can be proved through non-clinical evaluation;
3) Where safety and effectiveness of the medical device can be demonstrated through the analysis and assessment made on the basis of the data obtained from clinical trial or application of an equivalent medical device.

Even though the above listed alternative approaches have been allowed, the criteria of equivalency have not been clarified. In April 2015 the CMDE issued the "Guideline on the Clinical Evaluation of Medical Devices" [25], which for the first time elucidated the criteria of equivalency and the requirements on different approaches for clinical evaluation. In summary, three different acceptable approaches have been explained in this guideline:

1) Exempted device – the (imported) product is equivalent to an approved device in China of the same exempted category;
2) Non-exempted device – but (imported) product is equivalent to an approved device in China;
3) Clinical trial.

The equivalency on items listed in *Table 10* below should be taken into consideration.

Equivalency on	**Equivalency to**		
	exempted device	**non-exempted device (non-active device)**	**non-exempted device (active device)**
Working principle	x	X	x
Structure	x	X	x
Manufacturing procedure		X	x
Production materials	x (especially human contacting materials)	x (including material brand, animal source material, allogeneic material, components, drug components, biologically active	x (including material brand, animal source material, allogeneic material, components, drug components, biologically active

		material, applicable standards)	material, applicable standards)
Performance requirements	X	x	x (performance parameters; function parameters)
Safety evaluation		x (including biocompatibility, biological safety, etc.)	x (including biocompatibility, biological safety, EMC, etc.)
Core function of software			x
Applicable national / industrial standards		x	x
Intended use	X	x (including intended population, application areas, human contact type, indications, disease stage and extend of indications, application environment)	x (including intended population, application areas, human contact type, indications, disease stage and extend of indications, application environment)
Method/Type of application	X	x	x
Contraindication		x	x
Caution and warnings		x	x
Sterilization	X	x	x
Packaging		x	x
Labelling		x	x
Instructions for Use		x	x
Delivery status		x	x

Table 10: Criteria of equivalency

As the table above shows already, to demonstrate the equivalency, the applicant has to provide for both the reference and new device the detailed information that is not publicly available, such as production materials, manufacturing procedure and applicable standards. In addition, when choosing the equivalency approach, a clinical evaluation report (CER) has to be provided as the alternative

document to the clinical trial report. The CER should also include the following, not publicly available information (note: translated into English by the author of this master thesis):

1) Non-clinical research data;
2) Literatures;
3) Clinical application experience data;
4) Complaints and adverse events;
5) CAPAs related to clinical risks;
6) Data from Chinese population;
7) Additional clinical study in China.

Due to restrictions from the availability of requested information and data from reference devices, it's not practical to choose the equivalency route when only similar products from competitors have been approved in China. It makes more sense to choose this approach when the same applicant has similar products or same products of previous generation that have been approved in China already. However, the significance of differences still has to be determined during the case-by-case review. In case of insufficient data, it would be very challenging to finish the additional clinical study within the 1-year deadline for supplement submission as restricted by Article 35 of the "Provisions for Medical Device Registration". The worst case could be withdrawal of the application due to insufficient data.

If the equivalency approach is not feasible, then clinical trial has to be conducted for class II and class III medical devices. However, in the EU, if the device is neither implantable nor in Class III, clinical trial is not always the first option to demonstrate its safety and efficacy. According to Article 23 of the "Provisions for Medical Device Registration", the clinical trial institution should be qualified in accordance with the Chinese "Good Clinical Practice", meaning only clinical trial data from qualified Chinese institutions would be accepted.

In 2018 the CFDA issued the final version of the "Guideline on Accepting Foreign Clinical Data", offering to simplify the application procedure for applicants with qualified non-local clinical trial data.

Chapter 4.2.1.1 of this thesis will further discuss the meaning and impact of this guideline.

4.1.6.2 Change application

Chapter 3.2.3.2 introduced the requirements for change applications for class II and class III medical devices in China. Although no explanation has been given in the “Provisions for Medical Device Registration”, not all changes can be approved through change applications. The “Guideline on Division of Registration Unit” should be taken into consideration when deciding whether the proposed changes may trigger a new application (= initial registration) in China. The key criteria will be the significance of differences between the technical principle, structure / component, performance criteria and application scope. However, whether the changes are significant enough to trigger a new application, interpretations from the applicant, the administrative service centre of the NMPA and different reviewers from the CMDE could be different. It is possible that an accepted change application being rejected during the technical review and a new application for the changed product has to be submitted instead.

In the EU, the manufacturer can always consult the notified body on the necessity of a change notification or the application for a new certificate. In China however, although the NMPA offers pre-submission consultation to applicants, the communication will be much more limited than that between the manufacturer and the notified body in the EU. As explained in the CFDA announcement on the implementation of pre-submission consultation [26], only very few appointments will be scheduled, and the applicant has to apply for an appointment far in advance. Also, the duration of consultation will be very short and only up to 5 questions are allowed to be posted by an applicant in each consultation. Furthermore, different offices from the CMDE will attend the consultation in rotation and only questions related to the responsibilities of the attending office can be asked during the consultation. Considering the uncertainties, it is recommendable to conduct the case-by-case assessment of the impact from proposed changes to existing approvals in China.

Regarding the dossier requirement, special attention should still be paid to the possible involvement of registration test and clinical evaluation. The

necessity of additional tests to be done in China should be evaluated thoroughly before the submission because it would be very difficult to finish them later within the 1-year deadline of supplement submission.

4.2 Recent changes indicating the new trend in Chinese medical device regulations

The publication of the “Provisions for Medical Device Registration” in 2014 has been followed by the publication of many other new regulations and revisions to existing regulations in China, some of which indicated very intriguing new trend. This chapter will discuss the most significant new changes in Chinese medical device regulations.

4.2.1 Clinical trial exemption

4.2.1.1 The acceptance of foreign clinical trial data

As mentioned already in section 4.1.6.1 of this thesis, clinical trial is a must for all class II and class III medical devices unless meeting the criteria of exemption according to the current “Provisions for Medical Device Registration”. However, it is difficult to get such exemptions, i.e., to obtain all the requested information to demonstrate the equivalency to devices that have been approved in China already. Hence the publication of the “Guideline on Accepting Foreign Clinical Data” is definitely good news to foreign applicants because due to the qualification of clinical trial institution, local clinical trial data will be necessary for imported class II and class III medical devices that cannot be exempted from clinical trials. However, this new guideline will not put an end to the need of local clinical trial data for imported class II and class III medical devices, but rather provides an alternative choice for those applicants with qualified existing data.

First of all, the data covered in this guideline should meet the following criteria (note: translated into English by the author of this master thesis):

- clinical trial data to assess the product safety and efficacy under normal use condition
- obtained from qualified clinical institutions
- for the same device that applies for approval in China

Secondly the data should be obtained following the basic requirements listed below:

- in accordance with the Helsinki Declaration;
- in accordance with the Chinese “Good Clinical Practice for Medical Devices” [28] (any discrepancy should be justified);
- the applicant and clinical trial institution should be the subject of supervision and inspection from the NMPA;
- the data obtained should be truthful, reliable and traceable and the complete data should be provided to the NMPA.

The data to be submitted to the NMPA should include at least the clinical trial protocol, conclusion from the ethic committee and complete clinical trial report with the analysis of the complete data and its conclusion.

If applicable Chinese guidelines on the same or similar product category include requirements on the clinical trial such as trial design, sample size and endpoints, the foreign data have to meet these Chinese requirements. And in case of discrepancies that cannot be justified, additional clinical study in China will be requested. The differences between factors such as races, living conditions and medical facilities that may affect the clinical trial result should also be taken into consideration and should be justified.

4.2.1.2 The challenges and opportunities

While providing an alternative approach to conducting local clinical trials in China, the data that may be accepted will be restricted to data with good quality from a full-scale clinical trial. However, in the EU, a full-scale clinical trial is not always the first option for medical device manufacturers. Hence this new guideline will not be helpful to manufacturers that have never conducted a full-scale clinical trial. Additionally, the MDD doesn’t require the clinical investigations for medical devices to be conducted in accordance with the GCP. Although the MDR now requires that clinical investigations for medical devices should be in line with the international standard ISO 14155:2011 (2) on good clinical practice, it should be noted that ISO 14155:2011 does not cover many aspects that have been required by the

(2) ISO 14155:2011, Clinical investigation of medical devices for human subjects -- Good clinical practice.

GCP that were primarily developed for clinical trials of medicinal products. It is also worth noting that although the Chinese GCP takes reference from the ICH Guideline on Good Clinical Practice [29], there are noticeable discrepancies aside from Chinese local laws and regulations. As an example, *Table 11* shows the discrepancies of requirements on the ethics committee (EC) between the Chinese GCP, the ICH Guideline and ISO 14155:2011.

	Chinese GCP	**ICH Guideline on GCP**	**ISO standard 14155:2011**
Composition of the EC	- At least five members, including members from medical and non-medical area and members of **different gender**; - At least one member of **legal occupation** among members from non-medical area. - At least one member who is independent of the institution / trial site.	(a) At least five members. (b) At least one member whose primary area of interest is in a non-scientific area. (c) At least one member who is independent of the institution / trial site.	N / A
Document retention	The EC should retain all relevant records for a period of at least **10**-years after completion of the trial.	The EC should retain all relevant records for a period of at least 3-years after completion of the trial.	N / A

Table 11: Discrepancies of requirements on the EC

Despite discrepancies, both China and the EU have been trying to harmonize the clinical trial requirements with international regulations. And since the CFDA became the regular member of ICH in 2017, the harmonization procedure in China has been accelerated. The publication of the “Guideline on Accepting Foreign Clinical Data” is CFDA’s first attempt to save unnecessary cost, time and effort for applicants who have already obtained solid data in compliance with recognized international regulations.

The applicant should carefully review the existing clinical trial data and analyse possible gaps between the relevant requirements in China and in the EU. If discrepancies cannot be fully justified, additional clinical study in China should be taken into consideration. CFDA recommended that the applicant should consult CFDA’s reviewer first before submitting registration applications with foreign clinical trial data only. Considering the 1-year deadline for the supplement submission, it would make sense to do some

pre-preparation works for possible additional clinical study in China before the submission, such as screening potential clinical study site(s), planning for budget and resource. In case additional clinical data have been requested during the review, the applicant should make full use of the very limited chances to discuss with the reviewer on the design and sample size of the clinical study and possible extension of the review time.

Now that the MDR also requires higher quality for clinical data, if planned in advance and covering the specific requirements from Chinese GCP in the clinical investigation protocol, there could be good chance of using the same clinical data for both the conformity assessment in the EU and the registration application in China.

4.2.2 Proposed clinical evaluation exemption for class II medical devices

In November 2017 the "Regulations for the Supervision and Administration of Medical Devices (draft version)" has been submitted to the state council of China. This draft version included many proposed revisions to the current “Regulations for the Supervision and Administration of Medical Devices”. One significant revision is to the requirement on clinical evaluation. *Table 12* compares the relevant articles in the current version and the proposed version of the above-mentioned regulations and in the current version of “Provisions for Medical Device Registration” (note: translated into English by the author of this master thesis).

"Regulations for the Supervision and Administration of Medical Devices"		**“Provisions for Medical Device Registration”** (2014)
Proposed version (2017)	Current version (2014)	
Article 17: … For application for registration of a class II medical device, clinical **evaluation** is **not** mandatory; For application for registration of a class III medical device, clinical evaluation is mandatory …	Article 19: … For application for registration of a class II or class III medical device, clinical **trial** shall be conducted…	Article 22: … For application for registration of a class II or class III medical device, clinical **trial** shall be conducted…

Table 12: Comparison of requirement on clinical evaluation

Due to some of the proposed revisions being very significant, the discussion on this new "Regulations for the Supervision and Administration of Medical Devices" is expected to take quite some time and there is no guarantee that all of the proposed revisions will be approved by the state council. However, this proposal indicated intriguing signs already. Firstly, clinical trial will no longer be the first option to apply for a registration certificate in China; compared to previously restricting to clinical trial only, the NMPA is now trying to accept alternative clinical evaluation approaches. Secondly, the NMPA is trying to further simplify the application procedure for class II devices; in addition to reducing the unnecessary cost, time and effort the applicants have to invest during the preparation phase, this could also lead to shorter review time for class II devices. Such positive attitude from the NMPA is definitely good news to all applicants, and especially to manufacturers of class II medical devices.

4.3 Alternative options to registration testing

The 2017 proposal of "Regulations for the Supervision and Administration of Medical Devices (draft version)" also includes the revisions to the documentation requirements on the submission dossier, in particular on the requirement of product test report (investigation of product's characteristics versus corresponding standards) and clinical evaluation. *Table 13* shows the differences between the proposed version and the current version (note: translated into English by the author of this master thesis).

"Regulations for the Supervision and Administration of Medical Devices"	
Current version (2014)	Proposed version (2017)
Article 9: The following documentation should be submitted for the filing of class I medical devices and the registration application of class II and class III medical devices: 1) risk analysis documentation; 2) product technical requirement; 3) product test report; **4) clinical evaluation documentation;** 5) product IFU and label sample; 6) quality system documentation	Article 9: The following documentation should be submitted for the filing of class I medical devices and the registration application of class II and class III medical devices: 1) risk analysis documentation; 2) product technical requirement; 3) product test report; 4) product IFU and label sample; 5) quality system documentation related to product development and manufacture;

related to product development and manufacture; 7) other data to demonstrate the product safety and efficacy. The applicant is responsible for the truthfulness of the submitted documentation.	6) other data to demonstrate the product safety and efficacy. The product test report may be the contract testing report from a qualified test institution or **self-testing report from the applicant or filing entity**. For applications of class II and class III medical devices that require clinical evaluation, the clinical evaluation report should be submitted. The applicant is responsible for the truthfulness, **completeness and traceability** of the submitted documentation.
Article 10 For class I medical devices, the product test report can be self-testing report from the applicant or filing entity; the clinical evaluation documentation does not require clinical trial report… …	Article 10 (integrated into Article 9) …
Article 11 … For class II and class III medical devices, the product test report should be registration testing report from a qualified test institution; the clinical evaluation documentation should include clinical trial report unless exempted.	Article 11 … (integrated into Article 9)

Table 13: Comparison of requirements on submission dossier

The revision on the requirements of clinical evaluation is in line with the proposed exemption of clinical trial for class II devices and further simplifies the documentation.

The seemingly simplification on the requirements of the registration test does not necessarily mean the exemption of registration testing. *Table 14* shows the requirements on registration testing from both the replaced version and current version of the "Provisions for Medical Device Registration" (note: translated into English by the author of this master thesis).

<table>
<tr><th colspan="2">"Provisions for Medical Device Registration"</th></tr>
<tr><td>Replaced version (2004)</td><td>Current version (2014)</td></tr>
<tr><td rowspan="2">Article 9

Class II and class III medical devices have to complete registration testing conducted by the test institutions qualified by both the State Food and Drug Administration and the General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China.

Clinical trials or registration application can be carried out only after the registration testing confirmed that the product complies with the product standard.

A list of qualified institutions will be published separately.</td><td>Article 16

When applying for class II and class III medical device registration, registration testing shall be conducted. The medical device testing institutions shall carry out relevant registration testing on the products in accordance with the product technical requirements.

The production of samples for registration testing shall comply with relevant requirements of quality management system for medical devices. Clinical trials or registration application can be carried out only after the products passed the registration testing.

For the filing of class I medical device, the filing entity may submit the product self-testing report.</td></tr>
<tr><td>Article 18

Medical device testing institutions shall have the relevant qualification of medical device testing, and perform testing within their specified testing scope. It shall carry out pre-evaluation of the product technical requirements. The pre-evaluation opinions together with the medical device registration testing report shall be issued to the applicant.

For the medical devices having not included in the testing scope of any medical device testing institutions, the corresponding registration department shall designate a testing institution which has the capability to conduct the testing.</td></tr>
</table>

Table 14: Requirements on registration testing

Considering that the registration test report has always been the crucial and mandatory document for medical device applications in China, and the test institutions have to be qualified by the authorities, it is in the opinion of the

author of this master thesis very unlikely that self-testing reports can be used to replace the registration testing report for class II and class III medical device applications. Additionally, the test institution that conducts the registration testing plays the very important role as the pre-reviewers of the PTR (replaced the previous product standard) as designated by the regulations. The pre-evaluation should cover the following aspects (note: translated into English by the author of this thesis): [30]

- the completeness and applicability of the performance criteria; the feasibility, repeatability and the suitability of the testing method;
- the completeness and applicability of the mandatory national standard and industrial standard and the suitability of the clauses being referred to;
- the feasibility, repeatability and the suitability of the referenced content from the China Pharmacopeia.

As the pre-evaluation should cover many China specific requirements, in case of self-testing reports, especially done by foreign manufacturers, there could be issues with the acceptability of the PTR.

Since April 2017 the registration testing fee has been cancelled [31], leading to long waiting time for registration testing procedures and delay of applications. This issue has been noticed by the CFDA already, stating that contract testing report will also be accepted for registration purpose, as long as the test has been conducted in accordance with the PTR and a pre-evaluation conclusion from the test lab has been included. [32] Considering that both the registration test and contract test are type testing conducted by qualified test institutions, and the pre-evaluation conclusion from the test lab is still a mandatory document for submissions in China, the proposed revision on the registration test requirement could be the attempt from the NMPA to accept other form of type testing for registration applications, rather than the sign of exempting type testing in China.

4.4 Post market surveillance being strengthened

According to Article 5 of the “Provisions for Adverse Events Surveillance and Re-assessment of Medical Devices”, the NMPA will establish a national surveillance system for adverse events of medical devices. Article 14 of the same “Provisions” requires the applicant to establish a quality management

system that includes adverse events surveillance and product re-assessment; the adverse events should be collected and reported in time and the product risk evaluation report should be updated periodically based on surveillance data. The trend of strengthening on medical device surveillance in China is in line with the trend in the EU. However, it is worth noting that adverse events occurred both within and outside China are required to be reported to the NMPA for imported devices. Therefore, if the products are being marketed both in China and in the EU, it would make sense to cover the new specific requirements in China when updating the post market surveillance system to meet the new MDR requirement.

Requirements for the “Marketing Approval Holders” (MAHs) of imported medical devices to report adverse events occurred outside China:

- Serious adverse events leading to the product being controlled should be reported to the NMPA within 24 h after the applicant being informed;
- Serious adverse events that may lead to serious injury or death of the patient should be reported to the NMPA within 30 days after the applicant being informed.

Additionally, the MAHs of imported medical devices should submit a periodical risk evaluation report to the NMPA according to the regulations, which should summarize and analyse the adverse events and surveillance data from both within and outside China to re-evaluate the risk and benefit of the product and record the risk control measures being taken.

According to the “Provisions for Recalls of Medical Devices” [33], the MAHs of imported medical devices should report recalls conducted outside China to the NMPA as well.

4.5 Overseas on-site audits to be conducted

Since December 2015 the CFDA started the implementation of overseas on-site audits. Reports from the 24 overseas on-site audits conducted in 2017 have been published by the CFDA on its website. According to the NMPA, 26 overseas on-site audits have been conducted in 2018 and all the audit reports will be published on its website. So far, 5 reports from the overseas on-site audits conducted in 2018 have been published already. [34]

In China, the harmonized standard ISO 13485:2016 [3] has been adapted into a recommended industrial standard YY / T 0287-2017 [4] and is not mandatory. The mandatory QMS regulation in China and the basis for overseas on-site audit is the “Good Manufacture Practice for Medical Devices” [35] (including its annexes [36] [37] [38] when applicable), covering the design, manufacture, sales and after sale services of medical devices to be and being marketed in China. In general, the “Good Manufacture Practice for Medical Devices” has no conflict with the GMP or ISO 13485. Because the on-site audit is to be conducted selectively, for initial application for registration of imported medical devices, the NMPA will accept the QMS qualification of the foreign applicants issued by the country of origin. Concerning applicants from the EU (including UK), an ISO 13485 certificate will be accepted as the manufacturer’s qualification by the NMPA. However, special attention should be paid to the China specific requirements that should be covered by the QMS for medical devices being or to be marketed in China. For example, the PTR and applicable Chinese standards should be included in the technical documentation according to Article 24 of the “Good Manufacture Practice for Medical Devices”. And to study the overseas on-site audit reports published by the CFDA is highly recommended. Among these 29 reports, the author of this master thesis found that aside from common QMS non-conformities, other common non-conformities specific to Chinese regulations have been found, including the items listed in *Table 15* below.

Non-conformity items	**Reports in total**
Chinese regulations not being (correctly) identified [**40**] [**41**] [42] [**43**] [44] [45] [46] [47] [**49**] [**50**] [**52**] [**53**]	12 [a]
Inconsistencies with the PTR / product standard [**39**] [**41**] [**43**] [46] [**51**] [**52**] [**54**]	7 [b]
Specifications / components being marketed in China without CFDA approval [**39**] [**49**]	2 [c]

(3) ISO 13485:2016, Medical devices -- Quality management systems -- Requirements for regulatory purposes

(4) YY/T 0287-2017, Medical devices — Quality management systems — Requirements for regulatory purposes (ISO 13845:2016, IDT*)

*IDT = identical

Chinese IFU and label not meeting CFDA requirements [42]	1
Clean room condition inconsistent with Chinese GMP [48]	1
Notes: *a) 7 reports on the manufacturers based in the EU (including the UK);* *b) 6 reports on the manufacturers based in the EU (including the UK);* *c) Both reports on the manufacturers based in the UK.*	

Table 15: Non-conformities to Chinese regulations

Considering that the ISO 13485 certificate from the manufacturer based in the EU (including the UK) is the mandatory qualification file to be submitted for applications of imported medical devices, the non-conformities listed in *Table 15* are good examples that the compliance with ISO 13485 will not be enough for the Chinese “Good Manufacture Practice for Medical Devices” and other related Chinese regulations. The European manufacturers have to identify applicable Chinese regulations as early as possible to ensure the regulatory compliance of their medical devices to be and being marketed in China.

It is worth noting that Chinese local medical device manufacturers have to pass the on-site QMS audit before submitting the applications for their products, while most of the medical devices manufacturers overseas have never been audited on site by the CFDA. The non-execution of on-site QMS audits to overseas medical device manufacturers is largely due to the restrictions from practical and political aspects, such as manpower and visa application. So far, China has no plan to join the “Mutual Recognition Agreements” or accept audit reports issued by conformity assessment bodies from other countries. Even though in reality the overseas on-site audits have to be done selectively, the medical device manufacturers have the responsibility to comply with Chinese regulations when marketing their products in China. Hence, the urgency of identifying and adopting Chinese regulations should not be measured by the “risk” of being selected for the overseas on-site audit.

4.6 Special review procedure for innovative devices

For initial registration application of imported medical devices in China, the approval from the country of origin has always been the basic requirement; it

is the mandatory document to be submitted as requested by both the previous (2004) version and current (2014) version of the "Provisions for Medical Device Registration", and by the current (2014) version of the "Regulations for the Supervision and Administration of Medical Devices". A positive sign from the proposed "Regulations for the Supervision and Administration of Medical Devices (draft version)" is the exemption on the marketing approvals from the country of origin (= valid certificate of a Notified Body for European applicants) for innovative medical devices. However, there are many restrictions on the qualification as an "innovative" device. *Table 16* below shows the provisions concerning the requirements of marketing approval from the country of origin in the current version (2014) and proposed draft (2017) of the "Regulations for the Supervision and Administration of Medical Devices" (note: translated into English by the author of this master thesis).

"Regulations for the Supervision and Administration of Medical Devices"	
Current version (2014)	Proposed version (2017)
Article 11: … For applications of imported class II and class III medical devices, the marketing approval from the country of origin for the product to be marketed in China should be submitted to the CFDA by the agent. …	Article 11: … For applications of imported class II and class III medical devices, the marketing approval from the country of origin for the product to be marketed in China should be submitted to the NMPA by the agent. For **innovative** medical devices that have not been marketed outside China yet, the marketing approval from the country of origin can be **exempted**. …

Table 16: Requirement on marketing approval from the country of origin

As the proposal showed already, the exemption will only apply to devices that have not been put on the market yet. Additionally, the NMPA also tightened the eligibility criteria to narrow down the applicants. In 2018 the NMPA issued the final version on the special review procedure of innovative medical devices, further restricting the qualified innovative medical devices to medical devices that have a Chinese patent and the qualification application should

be submitted within 5 years after the publish date of its Chinese patent. The qualification of the patent will be reviewed during the expert meetings.

Despite all the restrictions, the proposed exemption on the marketing approval from the country of origin is still a positive sign that China is trying to show more favour to innovative medical devices. And this is not the first positive sign. In 2014 the CFDA has already issued a draft on the special review procedure of innovative medical devices, enabling earlier interaction with the reviewer and reducing queuing time during the testing and review procedures for qualified innovative medical devices. Although such special procedure will be good news to manufacturers of innovative medical devices who want to market their products in China as soon as possible, the procedure itself emphasizes that the technical requirements will not be compromised and the necessary procedures will not be omitted, meaning that if the foreign manufacturers wants to put their innovative medical device onto the market of China soon, they should be prepared for the requests on conducting thorough tests in China; and while the queuing time during the testing and review procedures will be shortened, the actual procedures of the testing and reviews could not be accelerated. In fact, whenever expert meetings are involved, the technical review would most likely take longer time and additional testing requests are to be expected. Even so, the chance of early interaction with the reviewer and experts will be really helpful to optimise the test design and avoid unnecessary cost and time during the preparation and review phases.

5. Conclusion and outlook

Although compared to medical device regulations in the EU, the Chinese medical device regulations are relatively immature and are being revised more frequently, the trend indicates that China is attempting to simplify the application procedures and be more open to new medical technologies while strengthening on the post market surveillance.

For many years, in China, the marketing approval of a medical device would be largely based on local testing data, including local type testing data and local clinical trial data. Although it will take time to review the system to accept respectively to implement alternative approaches, the up to now respectively amended and new elaborated regulations have already shown positive signs. Now being a regular member of the ICH as well as a full member of the IMDRF, the NMPA actively tries to accelerate the procedure to adopt harmonized standards and get in line with international regulations. It is to be expected that the discrepancies between Chinese and EN ISO (= European and International) standards and EU and FDA regulations will be less significant in the future.

Regarding post market surveillance, now that the MDR also strengthens the requirements for medical devices being marketed in the EU, to improve the plan, implementation and documentation of the post market surveillance activities will be the major tasks of European manufacturers. Hence the gap between the requirements on post market surveillance in the EU and in China should be less significant if the manufacturer complies with the MDR.

Although the signs are positive, the reform of the medical device regulation system in China will definitely take time. And considering the economic and political differences, China specific requirements will still exist. For European medical device manufacturers that prepare to enter the market of China or have already been marketing their products in China, it is recommendable to keep up with the development of Chinese medical device regulations. The early and correct input of Chinese regulations will be the best approach to avoid unnecessary time, cost and effort in later stages. Identifying the correct Chinese requirement in the design phase will be more cost-effective than

trying to cover the gap later during the application phase (for details refer to chapter 4 of this master thesis).

Because the medical device regulations, guidelines and standards in China will be issued in Chinese only, language could be an issue to European manufacturers. However, it is not impossible for any foreign manufacturer to keep up with the new Chinese regulations, as long as the responsibilities of the agent have been clearly defined and the communication between the agent and the foreign manufacturer is efficient enough.

Table 17 and *Table 18* below list the latest version of some very important Chinese regulations and helpful guidelines for medical devices.

Regulations	Issue date	Effective date
Regulations for the Supervision and Administration of Medical Devices (Decree No. 650 of the state council)	2014-03-07	2014-06-01
Provisions for Medical Device Registration (Decree No. 4 of the CFDA)*	2014-07-30	2014-10-01
Provisions for Instructions and Labels of Medical Devices (Decree No. 6 of the CFDA)*	2014-07-30	2014-10-01
Good Manufacture Practice for Medical Devices	2014-12-29	2015-03-01
Good Clinical Practice for Medical Devices (Decree No. 25 of the CFDA)	2016-03-01	2016-06-01
Provisions for Recalls of Medical Devices (Decree No.29 of the CFDA)	2017-01-25	2017-05-01
Rules for Classification of Medical Devices (Decree No.15 of the CFDA)*	2015-07-14	2016-01-01
Medical Device Classification Catalogue	2017-08-31	2018-08-01
Provisions for Adverse Events Surveillance and Re-assessment of Medical Devices" (Decree No. 1 of the SAMR)	2018-08-13	2019-01-01
** English version available. Links given in "References".*		

Table 17: List of important Chinese regulations

Guidelines	Issue date
Guideline on drafting Product Technical Requirement	2014-05-10
Guideline on the Clinical Evaluation of Medical Devices	2015-04-01
Guideline on Division of Registration Unit	2017-11-17

Guideline on Accepting Foreign Clinical Data	2018-01-10
Guideline on Initial Registration of Imported Medical Devices	2018-09-30
Guideline on Change Application of Imported Medical Devices	2018-09-30
Guideline on Renewal Application of Imported Medical Devices	2018-09-30

Table 18: List of useful Chinese guidelines

6. Summary

While being an attractive market to foreign medical device manufacturers, China is also considered to be one of the difficult markets due to the Chinese specific and rapidly changing regulations. Especially since the former State Food and Drug Administration (SFDA) reconstructed into the China Food and Drug Administration (CFDA) in 2013, the medical device regulations in China went through many changes, including major ones. In 2014, two fundamental regulations, the "Regulations for the Supervision and Administration of Medical Devices" and the "Provisions for Medical Device Registration" have been revised and came into force. Subsequently other regulations have been revised and new regulations and guidelines have been issued as well, providing clarifications to critical issues such as the requirement on clinical evaluations. The CFDA attempted to better normalize the review and approval procedures for medical device applications.

In March 2018 the CFDA has been reconstructed into the National Medical Products Administration (NMPA), which is now under the supervision of the State Administration for Market Regulation (SAMR). The post market surveillance of medical devices in China will be strengthened. New changes to the medical devices regulations in China are to be expected.

This master thesis took a general but systematic review of the current medical device regulations in China that have come into force since 2014, analysing the gap between the regulatory requirements in China and in the EU, with the focus on application procedures. This thesis also identified some of the most intriguing new trend in the recent changes of Chinese medical device regulations and discussed the possible challenges and opportunities to be faced by European medical device manufacturers that comply already with the medical device regulations in the EU. According to the author’s opinion, even though China will remain challenging to foreign manufacturers for quite some time, the recent changes of Chinese medical device regulations indicated positive signs of better normalized procedures. Although language could be an issue, as long as the foreign manufacturers manage the communication with their local agents effectively, it’s not impossible to keep up with the regulation changes in China. Besides, identifying the local specific requirements as early as possible will definitely

be more helpful than trying to cover the gap later, which applies to any other markets as well.

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Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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