CFDA Updates: Regulatory Requirement on MD Clinical Evaluation

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Dr. Han has broad experiences from government agency, academies to medical industry. He worked for Chinese Academy of Medical Sciences, National Health Economics Institute of MOH. Then, Dr. Han entered into global high-tech medical industries including SJM, with various positions from manager, Asian-regional senior manager, general manager of quality & regulatory affairs, and government & key customer relations director. From 2010 to 2013, Dr. Han joined the world-wide largest pharmaceutical market research consulting company-IMS, leading the IMS China Institute.

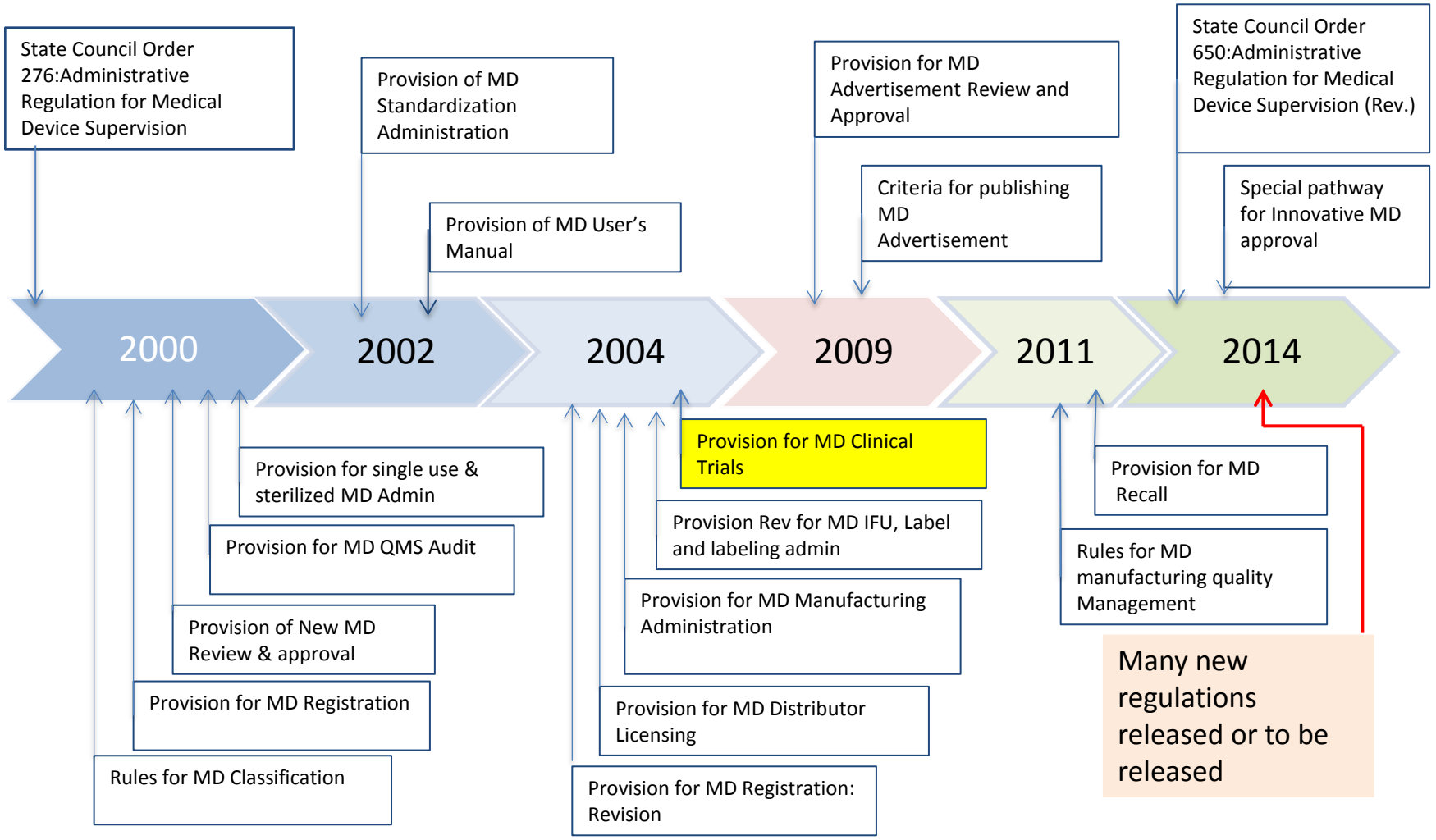
When employed by industry companies, he took many social roles respectively, including Chair, Medical Device Forum of American Chamber of Commerce in China; Chair, Health Equipment Working Group of European Chamber of Commerce; Co-Chair of Asian Harmonization Working Party in medical device regulations and standards and member of AHWP clinical investigation study group.

Dr. Han graduated from Tongji Medical University School of Public Health in 1984. From 1993 -1997, he studied at the University of Minnesota and earned the Master of Science in Health Services Research and Policy, and also completed his post-doctorate program in Epidemiology and Clinical Research.

CFDA updates: Clinical Requirements for Medical Device Registration

- Overview of Clinical Requirements from new regulations
  - Regulatory requirement for clinical evaluation
  - When clinical evaluation or trial is required
  - Difference approaches to meet clinical requirement
- How to meet clinical requirement without clinical trial
  - Demonstration of equivalency with a predicate
  - Proving safety and performance based clinical data obtained from equivalent product
  - What is contained in clinical evaluation report
- Requirement for conducting clinical trial
- Challenges from clinical requirement

Retrospection of CFDA Regulation Development



State Council Order No 650, enforced on June 1, 2014:
Regulation for MD Supervision and Administration

China Food and Drug Administration

Pre-Market

Post-Market

- MD Classification rules, 2000
- Innovative product Registration, 2014
- MD Registration, 2014
- Product IFU, Labeling, 2014
- Clinical Trials (GCP) in draft
- Manufacturing Quality, 2014
- Distribution/Sales, 2014
- Event report and recall, 2011
- Quality of MD in Use, in draft

New regulations are to put more strict control on high risk devices, relief low risk devices from over controls

A complete regulatory system is being developed

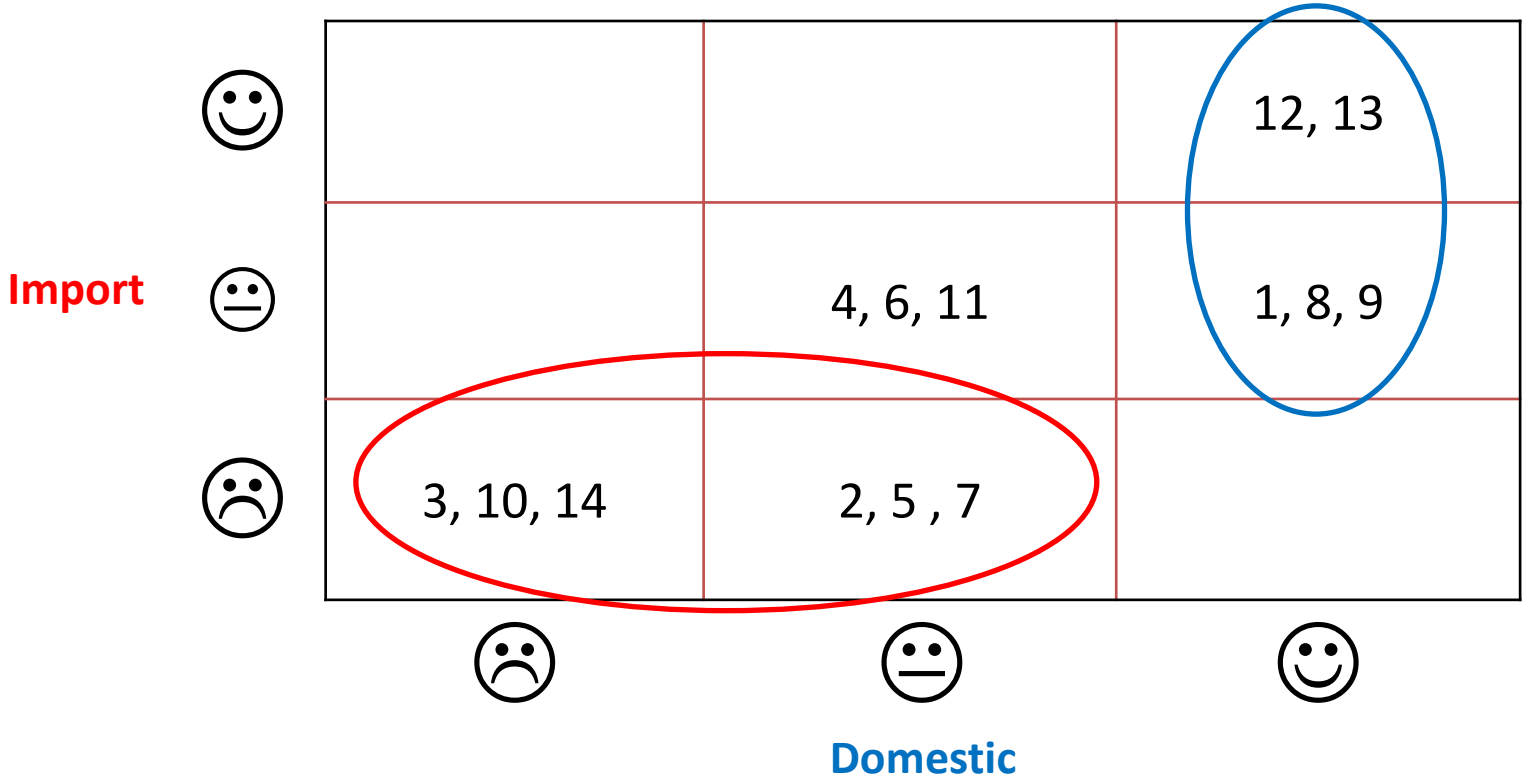
Main Changes from New Regulations for Market Approval (1 / 2)

	Before change	Change	Remarks
1	Almost the same registration process as class II and III	Technical evaluation not required for class I medical devices. Filing (listing) with CFDA is sufficient	Good for local but not really for import
2	Import devices are usually exempted for clinical trails	• More class II and class III devices are required to do clinical trials in China. • Exemptions are available through pre-determined exemption list or on application case by case	The biggest challenge to import device
3	Approval from CFDA generally not required for clinical trials	• CFDA pre-approval of Clinical trials (additional to Ethics) required for specified high risk class III devices. • Specified high-risk class device list recently published.	Longer time for registration
4	RPS required for testing and submission	Registration Product Standard (RPS) is not required for submission, but replaced with Product Technical files, which is closer to STED	More complicated - take care!
5	These are generally not required for import devices	Additional submission documents required including product risk management, product R&D, production information, and clinical literature (even if exempted from in-China trials).	More requirements for imports
6	Not required	Check list of essential requirement for safety & effectiveness must be provided in submission.	More scientific control
7	Large, heavy equipment may be tested after approval of registration	• Same as all other devices, large & heavy equipment must have been tested before registration application is submitted to CFDA. • For IVD, clinical trials only after passed Type testing.	Longer time for import registration

Main Changes from New Regulations for Market Approval (2 / 2)

No	Before change	Changes	Remarks
8	Applicant must have manufacturing license	Developer of an innovative device may apply for and receive registration certificate before mass production.	Good for local developer
9	CFDA handles all aspects of registration for all import and class III devices	CFDA may outsource some review tasks to provincial FDA or external technical organization (mainly for local applicants)	Good for local class III registration
10	60 working days for class II and III	Technical review timeline for class III device is prolonged to 90 working days. Class II remains 60 working days.	Longer class III device reviews
11	CFDA reviews all aspects of device even if submission just for change	CFDA technical evaluation of substantial changes will focus on change or modification only. Two change categories: 1) substantial change which needs evaluation and approval; 2) minor change which needs filing and recording.	Good trend
12	Registration lasts 4 years. Re-registration almost like initial registration	• Registration valid for five years • Renewal for extension, rather than re-registration must be submitted, and simpler than initial.	Good change
13	Registration number changes when device re-registered.	Registration Certificate is reformed, the initial registration number will be kept with device in life time, and attached with new change approval(s) if any.	Good change
14	No fee since 2004	Introduction of user fees for submissions and filings is planned. Fee schedule yet to be published.	Cost more

China State Council Order #650 : main changes and the impact on pre-market approval



In summary, the Amendments of regulations favour domestic manufacturers and toughen requirements for importers.

In-China Clinical trials and Pre-approval required for the trials of the high risk

	Before Change	After Change
Import device	- Not required to do in China - Clinical trials report if required in the manufacturer's country; - Clinical literature evaluation from the manufacturer's country	- Required to do in China if not in the exemption list or application for exemption not approved - May apply for exemption case by case - Pre-approval for clinical trials of high risk devices

Impact • Financial cost	• $ 0.5-1.5 millions for each of clinical trials for class III implantable MD • $300-700K clinical evaluation or supplementary trials even if exemption
• Time delay	19 months : 4 months for pre-clinical approval① 15 months for clinical trials, shortage② of clinical resource

Note ①: if the device is totally new to China market, or in the list of high-risk devices, it needs pre-approval. ②: constrains of clinical resources including patient, clinical centers, and research professional

CFDA Documents on MD Clinical Trails

Year	CFDA Documents related to clinical trials
2004.1	Provisions for MD Clinical trial
2012.8	Provisions for MD clinical trial quality administration in draft (GCP)
2014.8	Provisions for pre-approval of high-risk device clinical trial in draft
2014.8	Clinical trial exemption list of class III MD
2014.8	Clinical trial exemption list of class II MD
2014.8	Catalogue of high-risk class III MD for which clinical trial needs pre-clinical approval by CFDA
2015.5	MD clinical evaluation technical guidance released in May 2015
2015.7	Clinical trial needs to be filed with local authorities for quality inspection and control
2015.7	Accreditation for clinical trail institute (draft commented but not released)

CFDA Registration Requirement for clinical evaluation

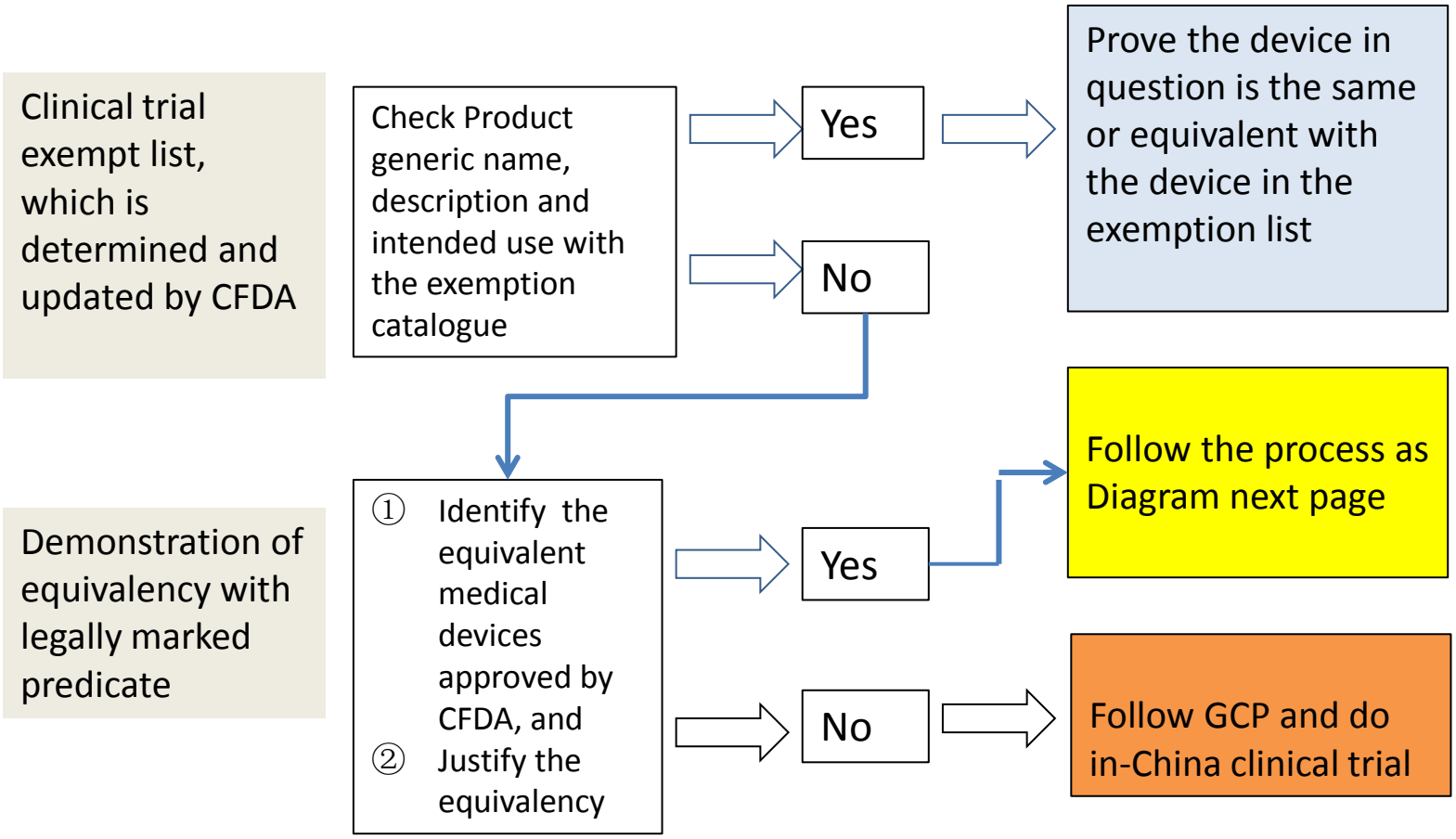
Chpt 4	New Regulation on MD Registration	Old Regulation on MD Registration
Art 20	Definition: a process for validation of clinical performance and intended use through clinical literature, application data, and clinical trials.	Art 16*, Class II &III registration, clinical trial information is required as Appendix table 12, where: only clinical information that was submitted in the country of origin should be provided.
Art 21	Clinical evaluation information is the documents that are composited to serve for clinical evaluation When clinical trial is necessary, the documents provided shall included clinical trial protocol and the report,	Art 18, when conducting a in-China clinical trial, clinical contract, protocol and report shall be provided.
Art 22	For the filing of class I device, no clinical trial is necessary. For registration of class II & III, clinical trial in China is required.	Art 17, When conducting a in-China clinical trial, the provision of MD clinical trial(CFDA order#5_2004 shall be compliant strictly.

Note*: In old regulation: When a new manufacturer who has never had a product legally marketed in China, in-China clinical trial is required only for registration of class III implantable device,

Three approaches to pass the clinical evaluation requirement

Approaches	Requirements
1) Through clinical trial exemption pre-determined by CFDA	For the medical devices which are included in the catalogues of clinical trial exemption, the clinical evaluation documents including the comparison with a predicate shall be provided for product registration.
2) Through • Demonstration of equivalency with a predicate legally market in China, and • Clinical evaluation based on the predicate	To submit clinical evaluation through the pathway of proving equivalency with the same type of CFDA-approved product, the applicant shall follow the requirements of CFDA Administrative Measures for Medical Device Registration to provide all information required for clinical evaluation.
3) Through conducting in-China clinical trial	To submit clinical evaluation through conducting clinical trial in China, the applicant shall provide the clinical trial agreement with the clinical center, approval of Ethic Review Committee, clinical trial protocol and clinical trial (medical) report 。

Three approaches to meet clinical requirements



Three approaches to meet the clinical evaluation requirement

Approaches
1) Through clinical trial exemption pre-determined by CFDA
2) Through • Demonstration of equivalency with a predicate legally market in China, and • Clinical evaluation based on the predicate
3) Through conducting in-China clinical trial

1) Demonstration of the product submitted (pending registration) is the product in the Catalogues of Clinical Trial Exemption.

2) Demonstration and Justification for equivalency of the product submitted (pending registration) with a predicate product legally marketed in China, and also with the comparison table (as attached) and relevant supporting documents.

The documents provided should prove the equivalency of the product submitted (pending registration) with the product from the exemption catalogues

Three approaches to pass the clinical evaluation requirement

Approaches
1) Through clinical trial exemption pre-determined by CFDA
2) Through • Demonstration of equivalency with a predicate legally market in China, and • Clinical evaluation based on the predicate
3) Through conducting in-China clinical trial

To submit clinical evaluation through the pathway of proving equivalency with the same type of CFDA-approved product, the applicant shall follow the requirements of CFDA Administrative Measures for Medical Device Registration to provide all information required for clinical evaluation.

Will talk about this in more details later

Three approach to pass the clinical evaluation requirement

Approaches
1) Through clinical trial exemption pre-determined by CFDA
2) Through • Demonstration of equivalency with a predicate legally market in China, and • Clinical evaluation based on the predicate
3) Through conducting in-China clinical trial

To submit clinical evaluation through conducting clinical trial in China, the applicant shall provide the clinical trial agreement with the clinical center, approval of Ethic Review Committee, clinical trial protocol and clinical trial (medical) report , and

To follow the GCP and pass the clinical audit by local FDA (clinical project filed with local FDA)

Purpose of Clinical Evaluation is the same through any one of approaches

In the clinical evaluation, the following clinical information shall be conformed, such as

- Scope of application
  - applicable population,
  - applicable site,
  - means of contact with human body,
  - indications for use,
  - degree and phase of disease and
  - application environment, etc.,
- Application methods,
- Contraindications,
- Precautions and warnings.

To reach the conclusion under normal using conditions:

- the product can reach desired performances;
- the risk of product is acceptable compared with the expected benefit;
- the product performance and safety can be properly supported by evidence.

When in-China clinical trial is required

three conditions for exemption

China's Order 650 requires clinical trial for class II and class III MD&D, but also outlines three conditions under which Class II and III MD&D to be exempted from clinical trials:

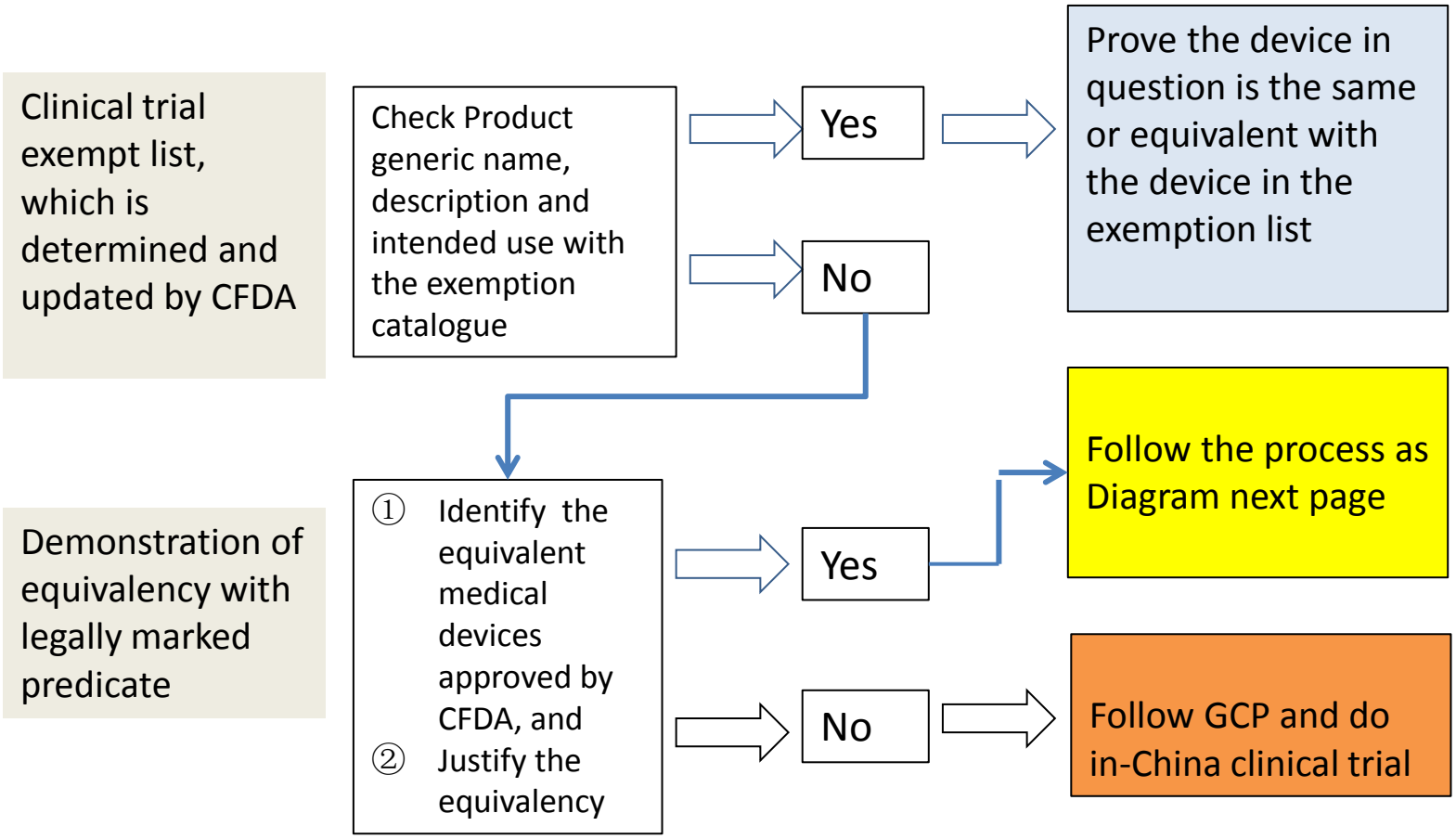
1. With **definite operating principle, established design, mature manufacturing process**, have no record for serious adverse event of substantially equivalent medical devices which have been marketed and clinically applied for years; and without changing the conventional purpose of use; -or-
2. The safety and effectiveness of the medical devices can be proven through **non-clinical evaluation;** -or-
3. The safety and effectiveness of the medical devices can be demonstrated through the analysis and evaluation on the data obtained from clinical trials or clinical application (clinical literatures) of the **substantially equivalent medical devices**, (which is legally marketed in China).

How in-China clinical trial may be exempted

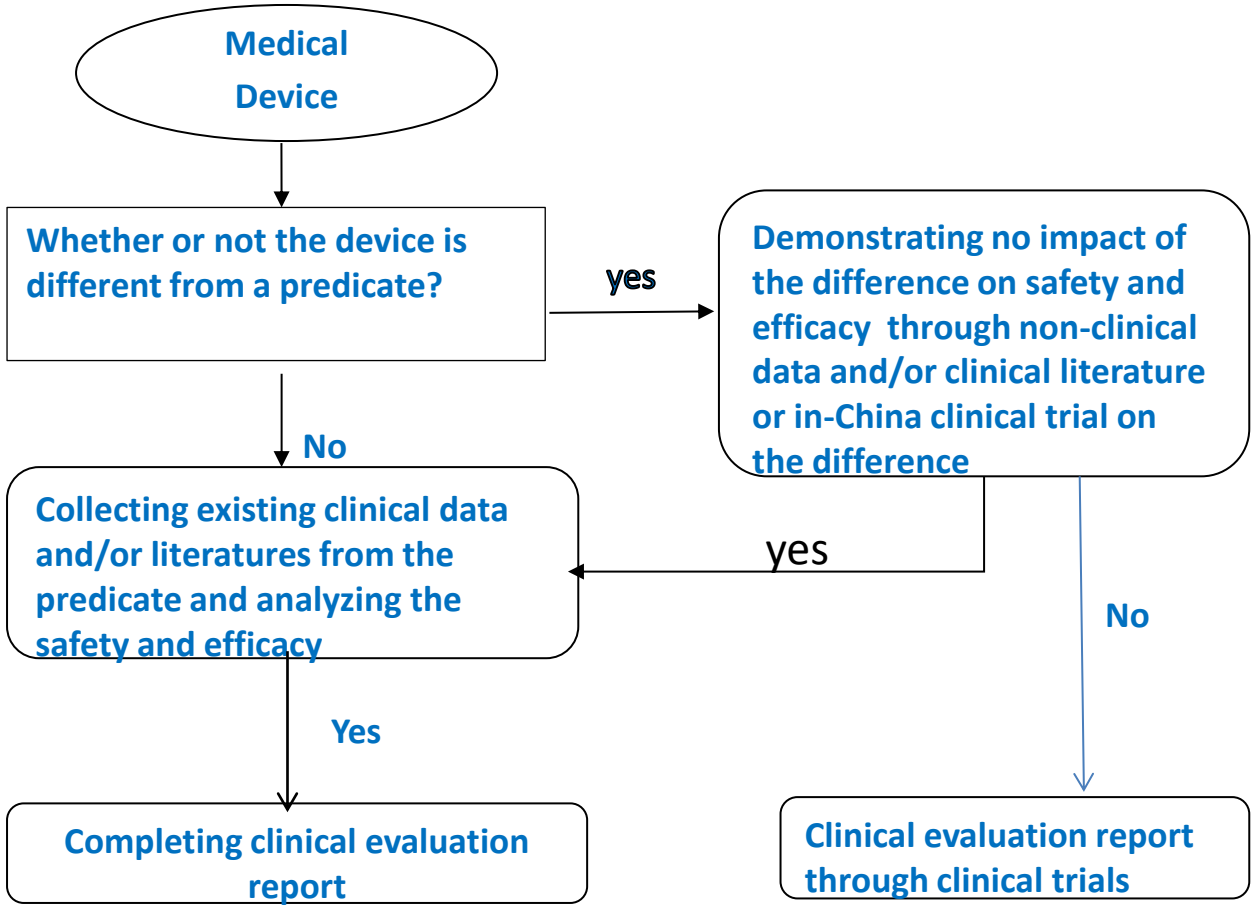
two ways for exemption

	Three conditions for exemption	
1	With definite operating principle, established design, mature manufacturing process, no record for serious adverse event of substantially equivalent medical devices marketed and clinically applied for years; and without changing the conventional purpose of use; -or-	Clinical trial exempt list, which is pre-determined and updated by CFDA
2	The safety and effectiveness of the medical devices can be proven through non-clinical evaluation; -or-	
3	The safety and effectiveness of the medical devices can be demonstrated through the analysis and evaluation on the data obtained from clinical trials or clinical application of the substantially equivalent medical devices.	Demonstration of equivalency with legally marked predicate

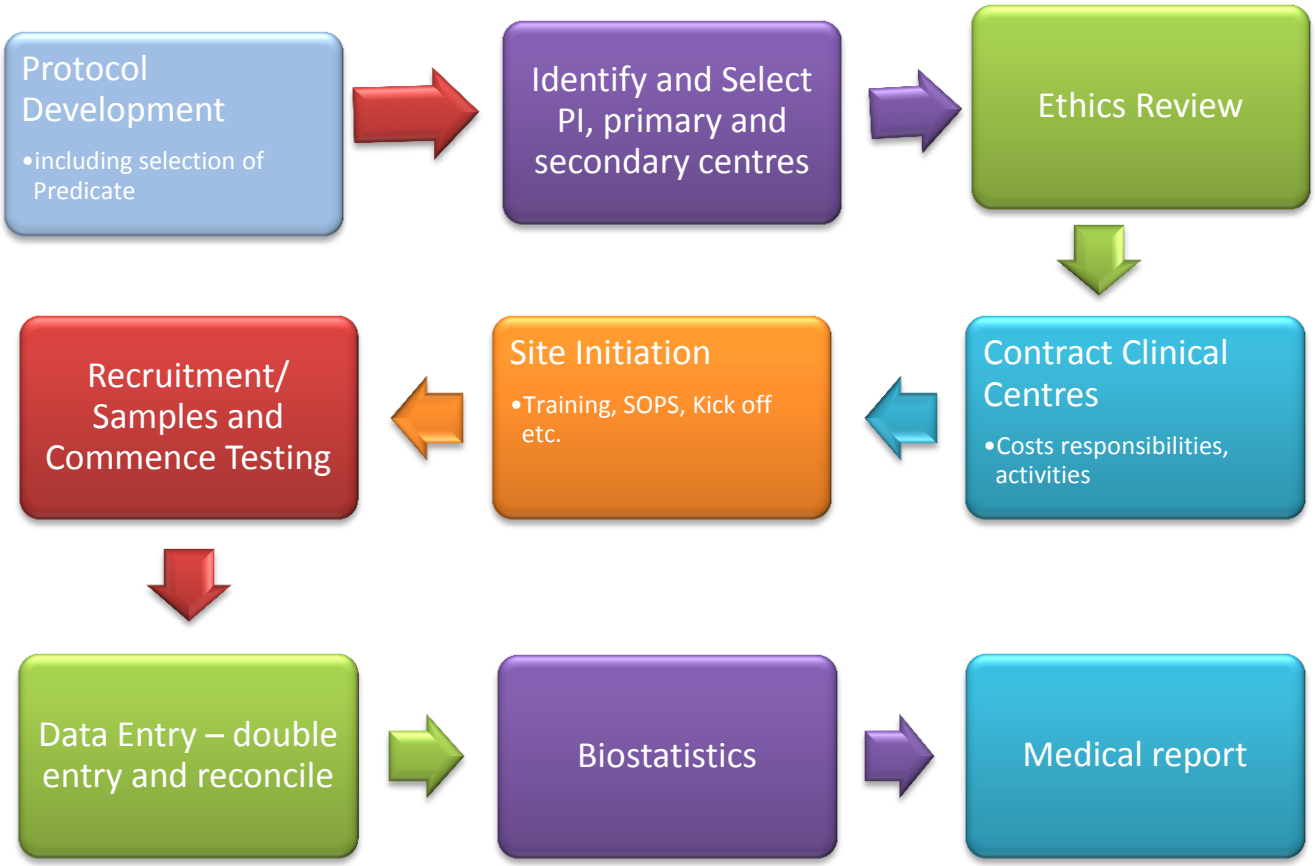
Three approaches to meet clinical requirements



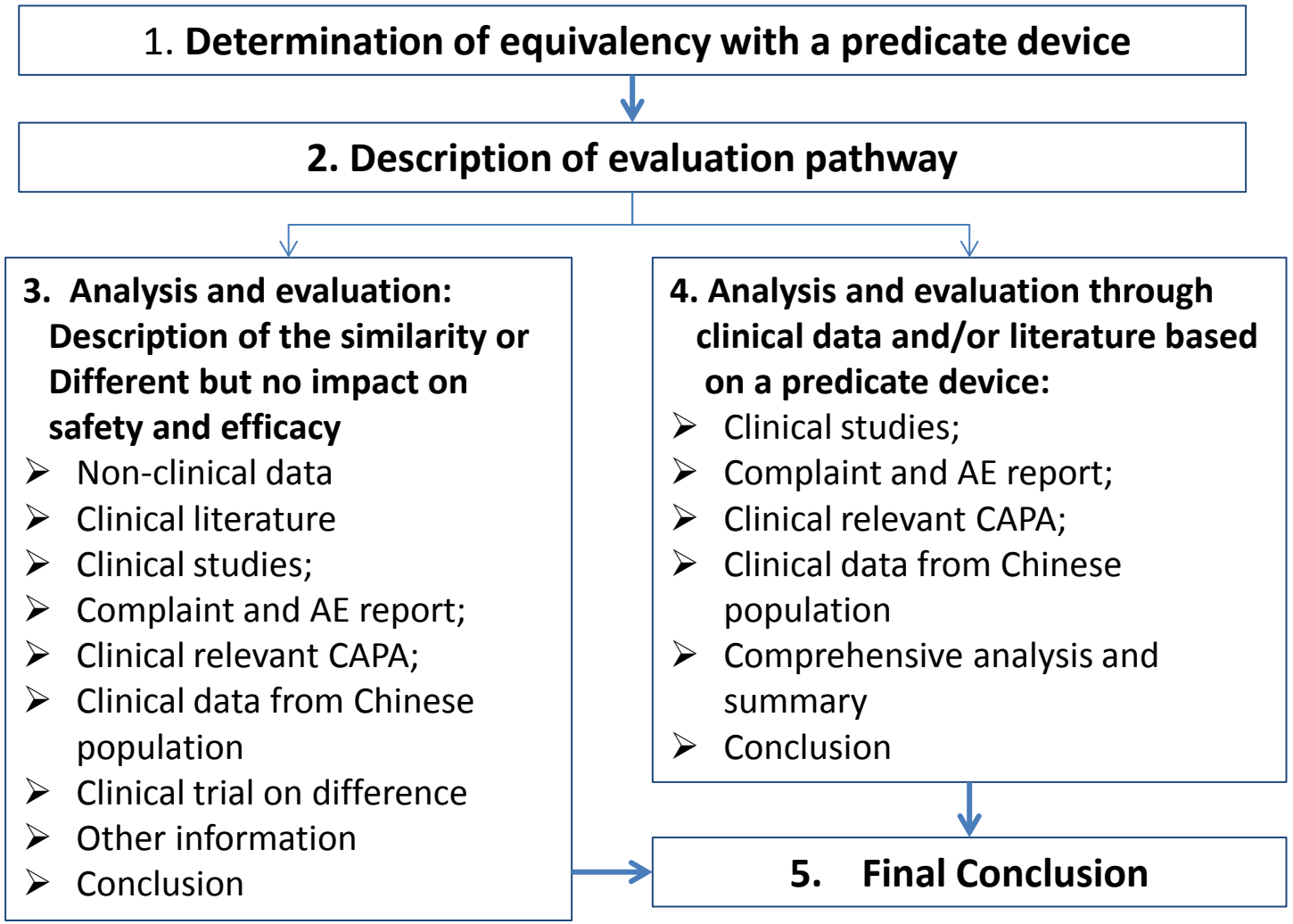
Clinical evaluation through analysis & evaluation on clinical trial or application of equivalent product



Overview of in-China **Trial** Process



Contents for clinical evaluation report-CFDA Guidance



Contents for clinical evaluation report – EU example

1. **General Details**
2. **Description of the Medical Device and Its Intended Application**
3. **Intended Indications for use and Claims**
4. **Context of the Clinical Evaluation**
5. **Summary of Clinical Data**
6. **Clinical Data Analysis**
7. **Conclusions**
8. **Signature and Attestation of Clinical Evaluator**

Detail Description

- Medical Device Proprietary Name:
- Manufacturer:
- Date of Clinical Evaluation Report:
- Name and Title of Clinical Evaluator:
- Qualifications of Clinical Evaluator:
- Description of the Medical Device and Its Intended Application

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Detail Description

- **Medical conditions to be treated**
- **Performance and safety standards applied**
- **Specific Safety and Performance Claims:**
  - General statistical information of use,
  - Volume of units and number of patients.
  - Main advantages of the product

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Detail Description

- Objective
- Summary of Device Technology
- Scope of Clinical Evaluation:
- Sources and Selection of Clinical Data:

➢ Type(s) and Source(s) of Clinical Data
- clinical and technical peer-reviewed journal articles,
- books chapters and other articles

➢ Published Literature Search and Selection
- Name and title of person conducting the literature search
- Qualifications of the person conducting the search
- Time period covered by the search
- Description of literature search and selection
- Objective of literature review

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Detail description

Description of literature search and selection

- A Medline-based search
- Key words for search
- The inclusion /exclusion criteria

List the key areas of product applications, for each of areas:

- A brief summary of the published literature
- Grouped by treatment areas
- Different complications, and responses.
- A complete bibliography

The main findings and conclusions from the literature referenced,
List of bibliography

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Detail description

General evaluation

Performance:
- Feasible treatment
- Advantage

Safety:
- Biocompatibility
- Risk evaluation
- Complaints and post-market surveillance
- Complications vs benefit

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Detail description, e.g.

This clinical evaluation documents the safe and effective performance of the product for its intended use. The clinical benefits of using for treating xxx are well established and, given appropriate precautions, outweigh the known risks or complications. The product does not fundamentally change these risks, as the underlying mechanism of the treatment is not altered.

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Pre-approval required for clinical trial of high risk MD

- Provisions for pre-approval of high-risk device clinical trial in drafted in 2013
- Class III MD list for which a clinical trial needs pre-clinical approval, released in 2014
- Application for pre-clinical approval should include:
  - Pre-clinical study report
  - Pre-clinical type test report against product standards applicable
  - Ethic review and approval
  - Market approval from the country of origin
  - Clinical trial protocol
  - Others
- It will take about 60 working days for technical review and final approval

Class III medical devices for which a clinical trial needs pre-approval from CFDA

No.	Product name	
1	Totally new design and new scope of application	Implantable pulse generator Implantable Cardiac Defibrillator Implantable cardiac resynchronization Defibrillator
2		Implantable blood pump
3		Implantable drug infusion pump
4	Intravascular stent system which not yet marketed in China	
5	Implantable artificial organs which not yet marketed in China Contact artificial organs Orthopedic fixation products and Orthopedic filling material	
6	Absorbable long bone fixation products	
7	Nano orthopedic implants	
8	Customized (3D printing) orthopedic implants	

General Requirements for clinical trial

- MD&D for clinical trial must have passed the **pre-clinical type tests** against applicable standards;
- MD&D and medical procedure in trial should be **free of charge** to patients enrolled;
- Provisions and guidance are not applicable for **post-market clinical studies,** which not considered as pre-market clinical trial
- Clinical trial shall be **filed with local authority** in the province where the trial is conducted, so may need to establish a full sample record traceability and archive;
- **Quality audits** by local FDA
- Conducted by a qualified clinical institute **CFDA-accredited**.

Key Challenges from clinical requirement

- **Availability of clinical data** obtained from the clinical trial and application of equivalent product of competitor – for equivalency approach
- **Availability of predicate device,** legally marketed in China – for comparison study
- **Sudden increase of clinical trial** projects would result in shortage of clinical resource, including clinical experts, subjects, clinical research professional
- **Accreditation** of clinical centres, for some rare diseases
- **Pre-submission consultation** – no particular process for clinical trial consultation, only by chance

Clinical requirement for medical device registration

Thanks ! Welcome for any Questions

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