China IVD Registration: Overview & Updates

China Med Device
Life Science Bridge

China Med Device, LLC

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Who we are: turnkey solutions to China

- **Regulatory Services from RA to QA**
  - Complete product life cycle: registration, type testing, CER/CRO, cGMP, AE, recall, inspection, and GSP
  - Legal Agent
- **Market Access Services**
  - Market Research and Reimbursement
  - Distribution & Partnership

Turn key solution for Western Medical Device & IVD Companies Entry & Growth to China

More…

Our Beijing Team

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Our Management Team

Grace Fu Palma – US CEO

Grace, a seasoned medtech executive, specializes in helping U.S. medical device companies to accelerate their commercialization in China. With 20+ years of experience driving product strategy, regulatory approval, business and channels partnership and market development for both large multinationals and startup companies, she held a variety of marketing and strategic development management positions.

Tony Liu – China CEO

Tony has over 15+ years of experience in the medical device industry. He has R&D and product management experience at multinationals and start-up firms in China as well as CFDA regulatory approval and GMP. He has led over 400 CFDA registrations. His product knowledge includes PET-MR, MR guided HIFU, Surgical Robotics in biopsy guidance, and endoscopes.

- Bi-lingual and bi-culture staff
- Offices in Boston, Beijing & Suzhou
- Strong connection with NMPA (CFDA)
- 1,000+ certificates
- 100+ years of accumulated experience with management team
- Turnkey solution from RA to QA: type testing, CER/CRO, cGMP…

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Agenda

- NMPA (CFDA) Overview and Important Update
- IVD Pre-Registration - Strategy
  - Classification Rules & Registration Unit
- IVD Registration
  - Type Testing
  - Clinical Trial Requirement
  - Clinical Exempt Requirement
- Registration Dossier (IVD Reagents)
  - Pathway

NMPA (CFDA) Unique Requirements

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Home country approval	Renewal every 5 years	Classifications: Different from FDA and CE
Type testing in NMPA approved centers	Chinese technical standards	Overseas clinical: ethnic difference

IVD Regulations: Device + Reagents

IVD Device Regulations

Administrative measures for the registration of Medical devices (NMPA, No. 4th)
Standard for quality management of clinical trials in medical devices (NMPA, NHFPC, No. 25th)
Regulations on the management of medical devices ' instructions and labels (NMPA, No. 6th)
Generic Naming Rules for medical devices (NMPA, No. 19th)

IVD Reagents Regulations

Administrative measures for the registration of in vitro diagnostic reagents (NMPA, No. 5th)
Amendment to the administration of the registration of in vitro diagnostic reagents (NMPA, No. 30th)
Technical guidelines for the clinical trial of in vitro diagnostic reagents (2014 Appendix 16th)
Guidelines for the preparation of an in-vitro diagnostic reagent specification (2014 Appendix 17th)
Requirements for registration of in-vitro diagnostic reagents and document format for approval (2014 Appendix 44th)

2017 & 2018 Major Updates

Change Faster Than Plan

Major NMPA (CFDA) Updates 2018

Draft Guideline on Accepting Medical Device Overseas Clinical Data (Jan 11)

Standardization Plan for Medical Devices (2018-2020) (Jan 29)

- Updating 300 + standards in next 3 years

3D printed medical device draft guideline (Feb 26)

- Only ask 10 to 20 pairs of observatory study if no predicate device
- 3-month follow up period to determine the observatory clinical benefits

UDI Implementation Plan (draft) (Feb 27)

Hainan special zone policies (Apr 9)

- First province for imported medical device approval
- Notify the approval within 7 days

Chairing initiative “Medical Device Clinical Evaluation Study” in IMDRF meeting (Apr 10)

Innovation Approval Procedure for Medical Devices (May 7)

Major NMPA (CFDA) Updates 2018

Interpretation on Medical Device Multi-Center Clinical Trial (Jun 1)

- One site can be designated as leading site in multi-center

4th Batch of Clinical Exemptions for Medical Devices and IVDs (Jun 11)

- 1st group of class III IVD exemptions: 31 cancer biomarkers
- A total of 1466 medical devices and IVDs exempted since August 2014

Regulation for Imported Medical Device Legal Agent (Draft) (Aug 3)

- Conduct yearly self-inspection for overseas manufacturers and itself
- Assist manufacturers to meet requirements for conditional approval
- Responsible for Chinese IFU

Initiation of Registration Holder System for Medical Devices in Guangdong and Tianjin (Aust 16)

- Shanghai initiated Jan 2018

Medical Device Pre-Assessment during Supplement Phase (Sep 12)

- know in advance if you meet the supplemental requirements

IVD Regulation Updates

8 new IVD regulations issued in 2017 & 2018

Issue Date	Implementation Date	Name
12/29/2017	3/1/2018	Announcement on the properties and category adjustment of allergen, flow cytometry, immunohistochemistry and in-situ hybridization.
12/29/2017	3/1/2018	Flow Cytometry Reagents Classification Catalogue
12/29/2017	3/1/2018	Immunohistochemical and in situ hybridization IVD reagents Classification Catalogue
09/30/2018	09/30/2018	Clinical exempt IVD reagents catalogue
11/8/2017	11/8/2017	Clinical evaluation requirements for clinical exempt IVD reagents
12/29/2017	3/1/2018	Non-medical device product catalogue
2/8/2017	2/8/2017	Amendment to the registration management method for in vitro diagnostic reagents

IVD Standard Updates

- 49 new IVD standards were issued in 2017
- Examples of involved IVD categories:
  - ✓ Labeled immunoassay
  - ✓ Colloidal gold method
  - ✓ Western blot
  - ✓ Immunoturbidimetry

Issuance Date	Implementation Date	Standard No.	Standard Names
12/11/2017	12/1/2018	YY/T 0588-2017	流式细胞仪
12/11/2017	12/1/2018	YY/T 1585-2017	总25-羟基维生素D测定试剂盒（标记免疫分析法）
12/11/2017	12/1/2018	YY/T 1591—2017	人类EGFR基因突变检测试剂盒
12/11/2017	12/1/2018	YY/T 1595—2017	氯胺酮检测试剂盒（胶体金法）
12/11/2017	12/1/2018	YY/T 1596—2017	甲型流感病毒核酸检测试剂盒（荧光PCR法）
12/11/2017	12/1/2018	YY/T 1597—2017	新生儿苯丙氨酸测定试剂盒
5/5/2017	4/1/2018	YY/T 1514—2017	人类免疫缺陷病毒（1+2型）抗体检测试剂盒（免疫印迹法）
5/5/2017	4/1/2018	YY/T 1515—2017	人类免疫缺陷病毒（I型）核酸定量检测试剂盒
5/5/2017	4/1/2018	YY/T 1517—2017	EB病毒衣壳抗原（VCA）IgA抗体检测试剂盒
5/5/2017	4/1/2018	YY/T 1525—2017	甲基安非他明检测试剂盒（胶体金法）
5/5/2017	4/1/2018	YY/T 1526—2017	人类免疫缺陷病毒抗原抗体联合检测试剂盒（发光类）
5/5/2017	4/1/2018	YY/T 1529—2017	酶联免疫分析仪
5/5/2017	4/1/2018	YY/T 1537—2017	放射治疗用激光定位系统性能和试验方法
5/5/2017	4/1/2018	YY/T 1549—2017	生化分析用校准物
4/1/2017	4/1/2018	YY/T 0654—2017	全自动生化分析仪
4/1/2017	4/1/2018	YY/T 0657—2017	医用离心机
4/1/2017	4/1/2018	YY/T 0659—2017	凝血分析仪
4/1/2017	4/1/2018	YY/T 1513—2017	C反应蛋白测定试剂盒
4/1/2017	4/1/2018	YY/T 1516—2017	泌乳素定量标记免疫分析试剂盒
4/1/2017	4/1/2018	YY/T 1518—2017	C-肽（C-P）定量标记免疫分析试剂盒
4/1/2017	4/1/2018	YY/T 1523—2017	二氧化碳测定试剂盒（PEPC酶法）
4/1/2017	4/1/2018	YY/T 1524—2017	α-L-岩藻糖苷酶（AFU）测定试剂盒（CNPF底物法）
4/1/2017	4/1/2018	YY/T 1527—2017	α/β-地中海贫血基因分型检测试剂盒
4/1/2017	4/1/2018	YY/T 1528—2017	肌红蛋白测定试剂盒（免疫比浊法）
4/1/2017	4/1/2018	YY/T 1530—2017	尿液有形成分分析仪用控制物质
4/1/2017	4/1/2018	YY/T 1531—2017	细菌生化鉴定系统
4/1/2017	4/1/2018	YY/T 1533—2017	全自动时间分辨荧光免疫分析仪
8/3/2016	6/1/2017	YY/T 1422—2016	血清妊娠相关血浆蛋白A检测试剂（盒）（定量标记免疫分析法）
8/3/2016	6/1/2017	YY/T 1482—2016	单纯疱疹病毒IgG抗体检测试剂（盒）
8/3/2016	6/1/2017	YY/T 1483—2016	单纯疱疹病毒IgM抗体检测试剂（盒）
4/29/2016	1/1/2017	YY/T 0589—2016	电解质分析仪
2/1/2016	1/1/2017	YY/T 1421—2016	载脂蛋白B测定试剂盒
2/1/2016	1/1/2017	YY/T 1423—2016	幽门螺杆菌抗体检测试剂盒（胶体金法）
2/1/2016	1/1/2017	YY/T 1424—2016	沙眼衣原体DNA检测试剂盒（荧光PCR法）
2/1/2016	1/1/2017	YY/T 1441—2016	体外诊断医疗器械性能评估通用要求
2/1/2016	1/1/2017	YY/T 1442—2016	β2-微球蛋白定量检测试剂（盒）
2/1/2016	1/1/2017	YY/T 1443—2016	甲型流感病毒抗原检测试剂盒（免疫层析法）
2/1/2016	1/1/2017	YY/T 1444—2016	总蛋白测定试剂盒
2/1/2016	1/1/2017	YY/T 1448—2016	脂蛋白（a）测定试剂盒
2/1/2016	1/1/2017	YY/T 1450—2016	载脂蛋白A-I测定试剂（盒）
2/1/2016	1/1/2017	YY/T 1451—2016	脑利钠肽和氨基末端脑利钠肽前体检测试剂（盒）（定量标记免疫分析法）
2/1/2016	1/1/2017	YY/T 1452—2016	干式血液细胞分析仪（离心法）
2/1/2016	1/1/2017	YY/T 1454—2016	自我检测用体外诊断医疗器械基本要求
2/1/2016	1/1/2017	YY/T 1455—2016	应用参考测量程序对酶催化活性浓度赋值及其不确定度评定指南
2/1/2016	1/1/2017	YY/T 1456—2016	铁蛋白定量检测试剂（盒）
2/1/2016	1/1/2017	YY/T 1458—2016	抗甲状腺过氧化物酶抗体定量检测试剂（盒）（化学发光免疫分析法）
2/1/2016	1/1/2017	YY/T 1459—2016	人类基因原位杂交检测试剂盒
2/1/2016	1/1/2017	YY/T 1461—2016	缺血修饰白蛋白测定试剂（盒）
2/1/2016	1/1/2017	YY/T 1462—2016	甲型H1N1流感病毒RNA检测试剂盒（荧光PCR法）

IVD Technical Review Guideline Updates

16 new IVD technical review guidelines were issued in 2018

Technical review guideline on Insulin assay reagent
Technical review guideline on Apolipoprotein B assay reagent
Technical review guideline on Apolipoprotein A1 assay reagent
Technical review guideline on Homocysteine assay reagent
Technical review guideline on Alanine Amino transferase assay reagent
Technical review guideline on D-dimer assay reagent (Immunoturbidimetry)
Technical review guideline on C-peptide assay reagent
Technical review guideline on urinalysis reagent strip
Technical review guideline on epidermal growth factor receptor (EGFR) gene mutation assay
Technical review guideline on helicobacter pylori antigen/antibody assay
Technical review guideline on anti-human globulin assay
Technical review guideline on nucleic acid assay for enterovirus RNA
Technical review guideline on cell mediated immune response assay for mycobacterium tuberculosis
Technical Review Guideline on Methicillin-Resistant Staphylococcus Aureus (MRSA) Reagent
Technical Review Guideline on Chromosomal Abnormalities Detection Reagent
Performance Evaluation Guideline of Next Generation Sequencing (NGS) Based Cancer Biomarker

IVD Registration Strategy

Client Example: NMPA (CFDA) Strategy

- Domestic vs Imports
- Classification
- Product Naming and Composition
- Clinical Trial Exemption
- Regular Pathway
- Competitive Regulatory Status
- Customized Technical Requirements and Type Testing
- Budget, Timeline and Milestones

IVD Pre-registration

—— Classification Rules

IVD Classification Guidelines

- Medical Devices Classification Rules (CFDA No. 15th)
- Announcement on the releasing of the Class I Medical Device Catalogue (CFDA, No. 8th)
- Clinical Exempt Medical Device Catalogue (NMPA, Sep 30th 2018)

Medical Device Classification Update

New Classification Catalogue Implemented on Aug 1st, 2018

Very different from the previous catalogue, dividing medical devices (excluding diagnostic reagents) into 22 categories by application and product characteristics.

IVD Reagents Classification Guidelines

- Administrative measures for the registration of in vitro diagnostic reagents (CFDA No. 5th)
- Announcement on the issuance of IVD reagent catalogue (CFDA, 2013, No 242)
- Clinical Exempt IVD reagent catalogue (NMPA, Sep 30th , 2018)
- Announcement on the properties and category adjustment of allergen, flow cytometry, immunohistochemistry and in-situ hybridization. (CFDA, 2017, No. 226th)

Current IVD Reagents Classifications

Class I	Class II	Class III
• Microbial media • Specimen processing products	• Protein testing • Saccharide testing • Hormone testing • Enzyme testing • Vitamin testing • Esters testing • Inorganic iron testing • Drug or drug metabolon testing • Autoantibodies testing • Microbiological identification or Drug susceptibility testing • Other physiological, biochemical, or immunological testing	• Antigens, antibodies, or nucleic acid test • Blood grouping or tissue typing • Human gene testing • Hereditary disease testing • Stupefacient, psychotropic, medical toxic drug testing • Drug target testing • Tumor markers • Allergen testing

- **Blood Screening & Radionuclide Marking are regulated as drugs in China**
- **No laboratory development tests in China**

IVD Reagents Classification (Special Instructions)

- Class II reagents used for the diagnosis, adjuvant diagnosis, and treatment testing of tumor and hereditary diseases shall be registered as Class III
- Reagents used for the detection of narcotic, psychotropic, or medical toxic drugs and their metabolites shall be registered as Class III
- Calibrators and controls used with Class I reagents shall be registered as Class II
- Calibrators and controls used with Class II and Class III reagents, when registering separately, shall use the same classification catalogue as the reagent.
- For multiple calibrators and controls, the registration class shall be determined by the highest

IVD Pre-registration

—— Registration Unit

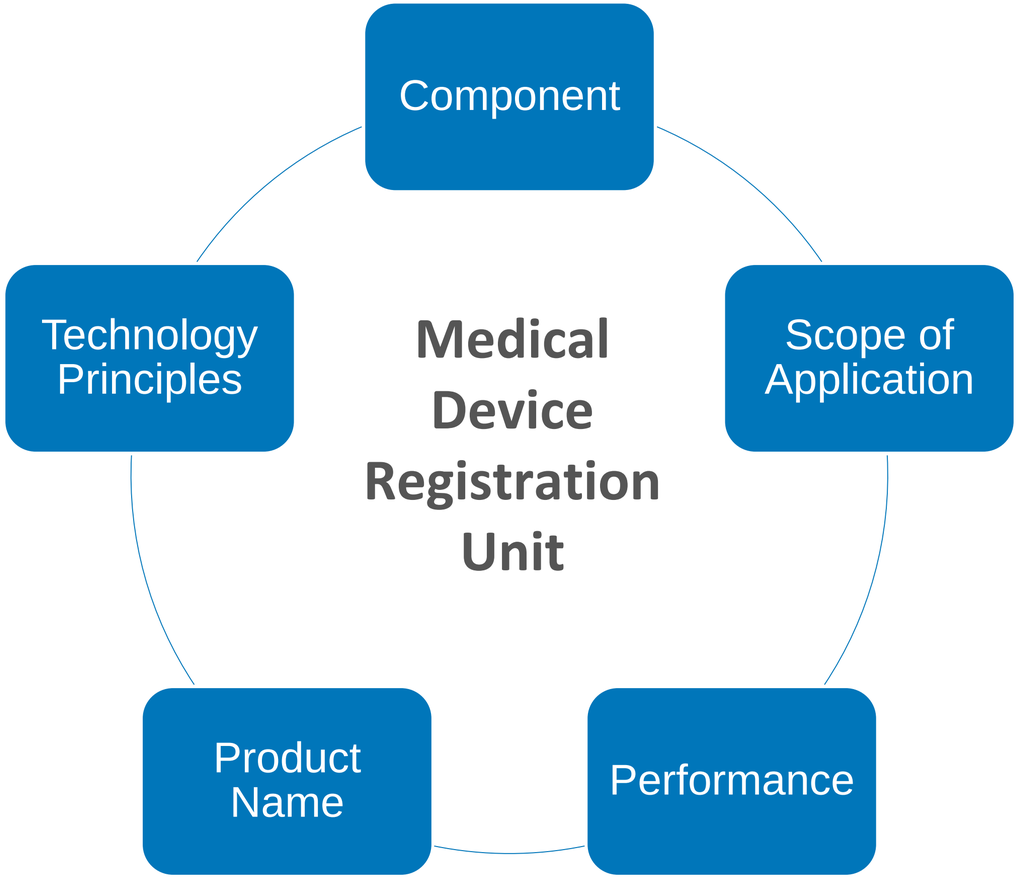
IVD Registration Unit Guideline

IVD device and reagent need to be registered separately

——Announcement on the issuance of medical device registration unit guideline (CFDA, 2017, No.187)

IVD Registration Unit —— Device

5 Key factors that affect the determination of a registration unit for medical device



IVD Registration Unit —— Reagent

Rule 1. A single registration unit may contain a single reagent or a kit

Rule 2. A single registration unit may contain multiple kits

Rule 3. Calibrators and controls can be registered with reagents or registered separately.

Rule 4. A single registration unit may contain different kit size or form

IVD Type Testing Report

- Issued by certified medical device testing centers
- It includes type testing report and product technical requirements pre-evaluation opinions.
- National standard product and reference panel shall be used for type testing if available.

IVD Type Testing

Technical Requirements Design

General Technical Requirements for IVD Devices

General Technical requirements include:

- Product model/specification
- Performance specs (physical, chemical, microbial)
- Test methods for performance specs
- Terminologies
- Appendix (complete model/specification list, special testing methods)

Reference order of standards

IVD Type Testing: Device & Reagent

IVD Devices

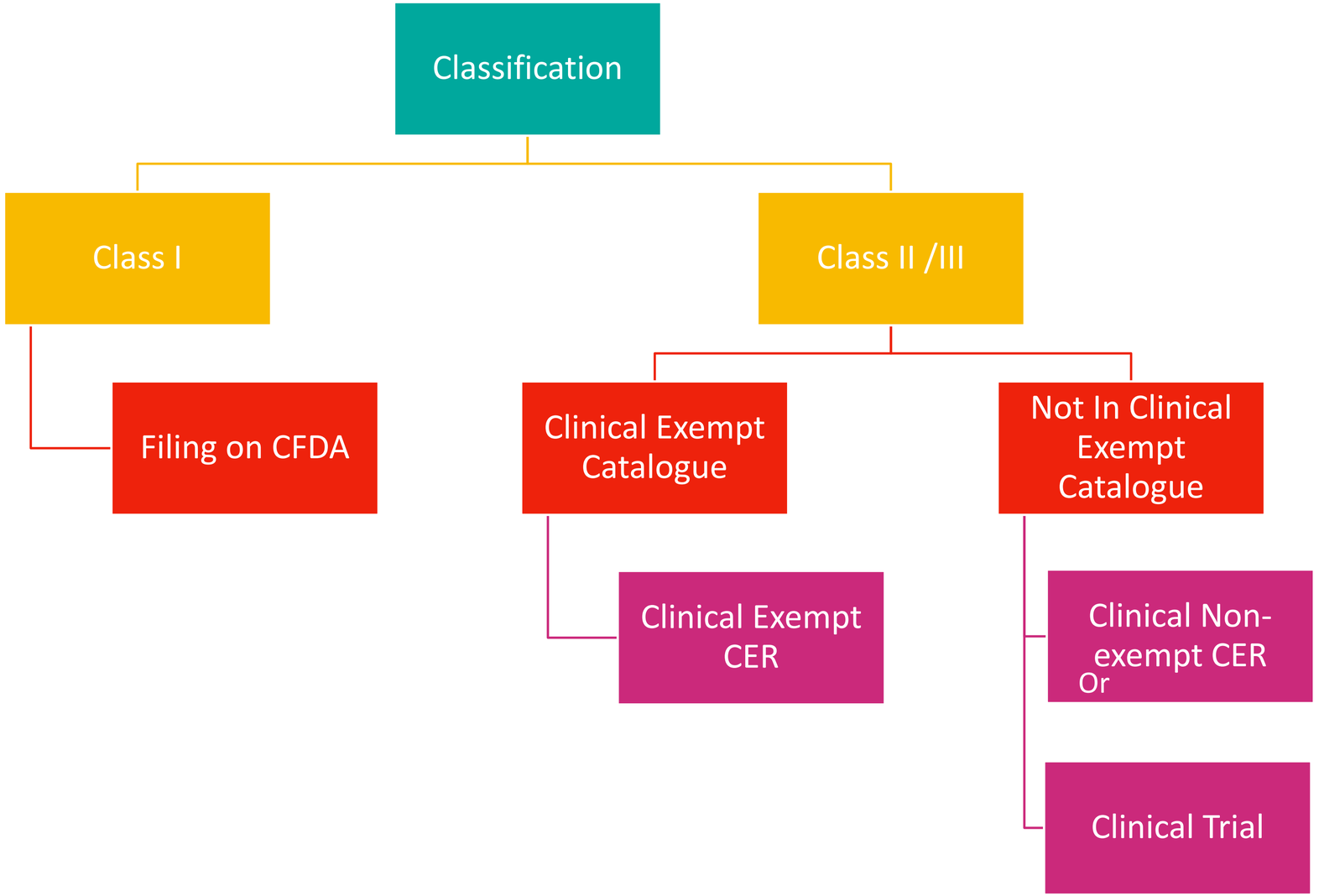
- Submit at least one product for testing.
- Need to pass EMC, safety testing, and testing with reagents

IVD Reagents

- Submit three continuous batches of samples for testing.
- Samples shall meet the relevant technical requirements and some may need to pass the accelerated aging test

Clinical Trial Requirements

Three Clinical Pathways In China



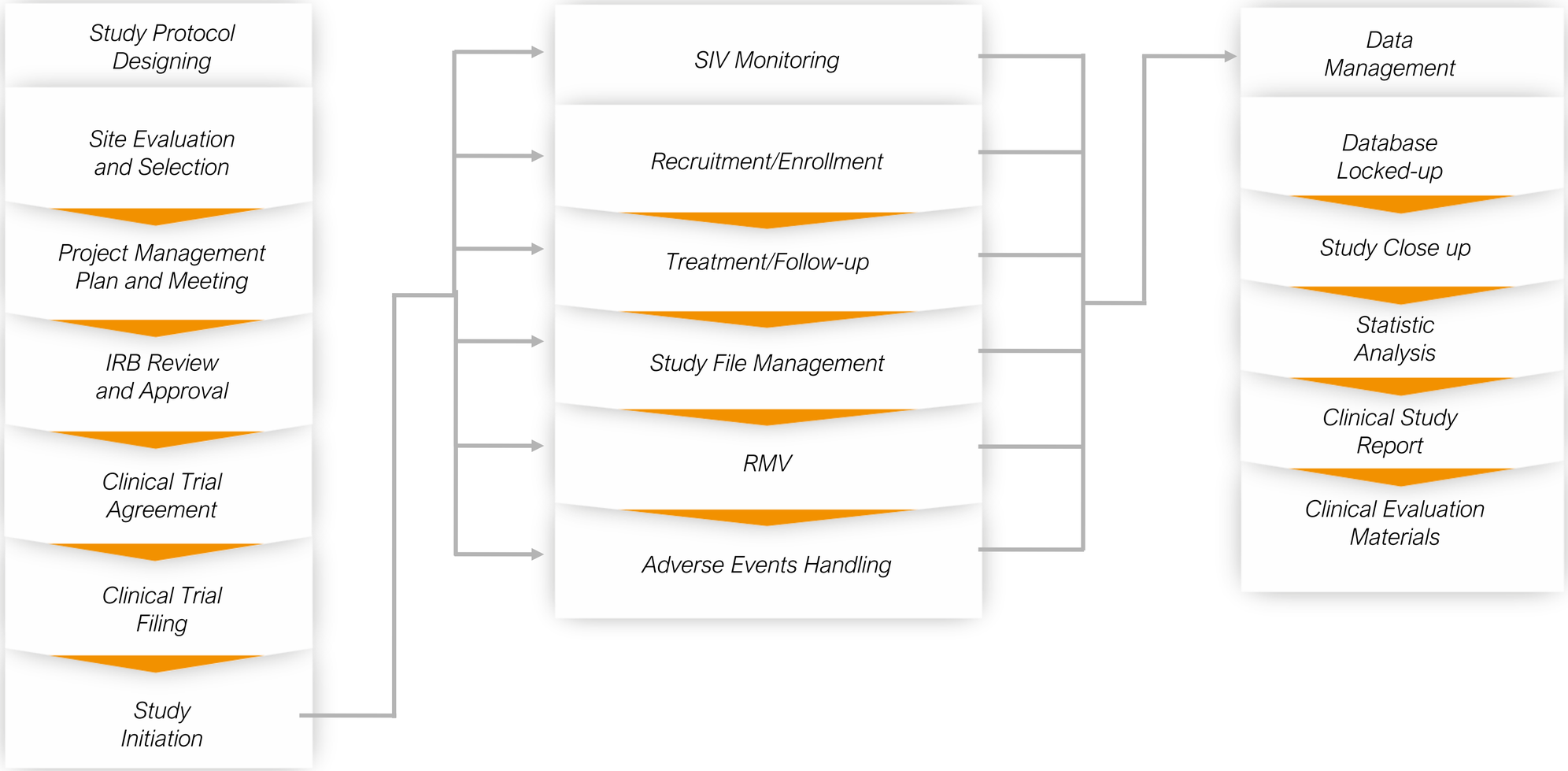
IVD Reagent Clinical Trial Guidelines

1. Administrative measures for the registration of IVD reagents
2. Requirements for the registration materials of IVD reagents
3. Technical guidelines for clinical trial of IVD reagents
4. Released guidelines for specific products:
   - Tumor markers
   - Tumor genes for individualized treatment
   - Drug abuse testing reagents
   - Flow cytometry kit
   - Pathogen IgM
   - Torch antibody
   - Hepatitis B virus nucleic acid assay
   - Hepatitis C virus nucleic acid assay
   - Human erythrocytes anti-stereotypes reagents
   - HIV
   - HPV
   - TB

No clinical trial needed for Class I

Class II & Class III may need clinical trials

Clinical Trial Process



Basic Requirements for IVD Reagent Clinical Trials

Subject Cohort Size

Class III ： 3 sites with >= 1000 patients

Class II: 2 sites with >= 200 patients

Pathogen detection by PCR: >= 500 patients

Flow cytometry: >=500 patients

Blood Grouping ： >= 3000

Newly developed IVD reagents ： >= 1000

Clinical Exempt Requirement

Clinical Exempt Catalogue — Device

Clinical Exempt Class II Medical Device Catalogue (CFDA, 2014, No. 12)

Clinical Exempt Class III Medical Device Catalogue (CFDA, 2014, No. 13)

Clinical Exempt Medical Device Catalogue (the 2nd batch) (CFDA, 2014, No. 133)

Clinical Exempt Medical Device Catalogue (the 3rd batch) (CFDA, 2017, No. 170)

Class II & III medical devices listed in the above catalogues are exempt from clinical trials. These products need to be compared with similar products for clinical evaluation.

Clinical Exempt Catalogue — Reagent

- The 3rd catalogue of clinical exempt IVD reagents (CFDA, 2017, No. 170)
- IVD reagents listed on this catalogue shall finish the clinical evaluation work in China as per the Clinical Evaluation Requirements for Clinical Exempt IVD Reagents (CFDA, 2017, No. 179)

Evaluation Pathways for Clinical Exempt IVD Reagents

- Compare with similar reagents in the market to prove the equivalence. (Comparison items include technical information, methodology, clinical indications, main performance index, calibrator traceability, etc.)

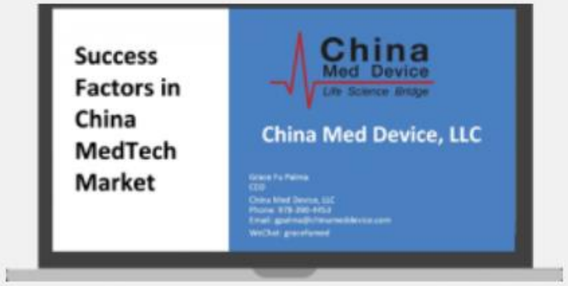
- Compare with reference method to prove consistency. CNAS certified laboratory shall be selected for the comparison research.

https://chinameddevice.com/webinar/

CFDA Key Updates GMP/QMS Overview

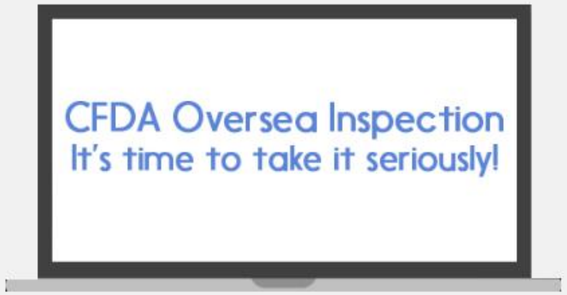
How To Get IVD Approval Through CFDA

Success Factors In China MedTech Market



Ingredients for Effective CFDA, CER & Clinical Trial

CFDA Oversea Inspection



Weekly and Monthly NMPA (CFDA) Roundups

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Monthly CFDA news roundup in policies, regulations, QA/recall/AE, and new approvals in medical device and IVD in China is brought to you by China Med Device, LLC. To schedule a complimentary consultation, please email info@ChinaMedDevice.com. To opt in for our monthly roundup, click HERE.

CFDA is expected to go through major structure changes as well as issuing more standards and guidelines in 2018 after the announcement of "Opinion of Deepening Reform of Review and Approval Policy to Encourage Medical Device/Drug Innovation" from the State Council of China central government in October 2017.

Direct Communication with NMPA (CFDA)

China Med Device, LLC Beijing Forum with NMPA

Beijing CFDA Training

Boston Meet CFDA Face to Face Meeting

Cambridge, Mass. – December 10, 2017 - China Med Device and CABA held a quarterly Regulatory Affairs event with CFDA representatives from Beijing in Cambridge, MA on Sunday, December 10.

Nearly 50 Regulatory representatives from U.S. Medtech companies, manufacturers, and industry consultants took advantage of the opportunity to meet and query two special guests from the CFDA; Director Bin Liu and Reviewer Yue Min from the Center for Medical Device Evaluation (CMDE).

Thank you!
Questions?

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