CFDA Jina Quality Suervision And Inspection Center For Medical Devices
Shandong Quality Inspection Center for Medical Devices

Regulations, Standards and Practices of Biocompatibility and Toxicology & Assessment in China

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SOT | Society of Toxicology
Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

Conflict of Interest Statement

- I am employed by Shandong Quality Inspection Center For Medical Devices
- The opinions stated are mine and do not necessarily reflect those of my facility

Agenda

- Registration and Biological evaluation in China
- Biocompatibility standards in China
- Practices and Future trends
- CFDA-Jinan Inspection Center

Regulation framework

Administrative and regulatory agency

Local Government CFDA

Local Government CFDA Review Centers

Technical support

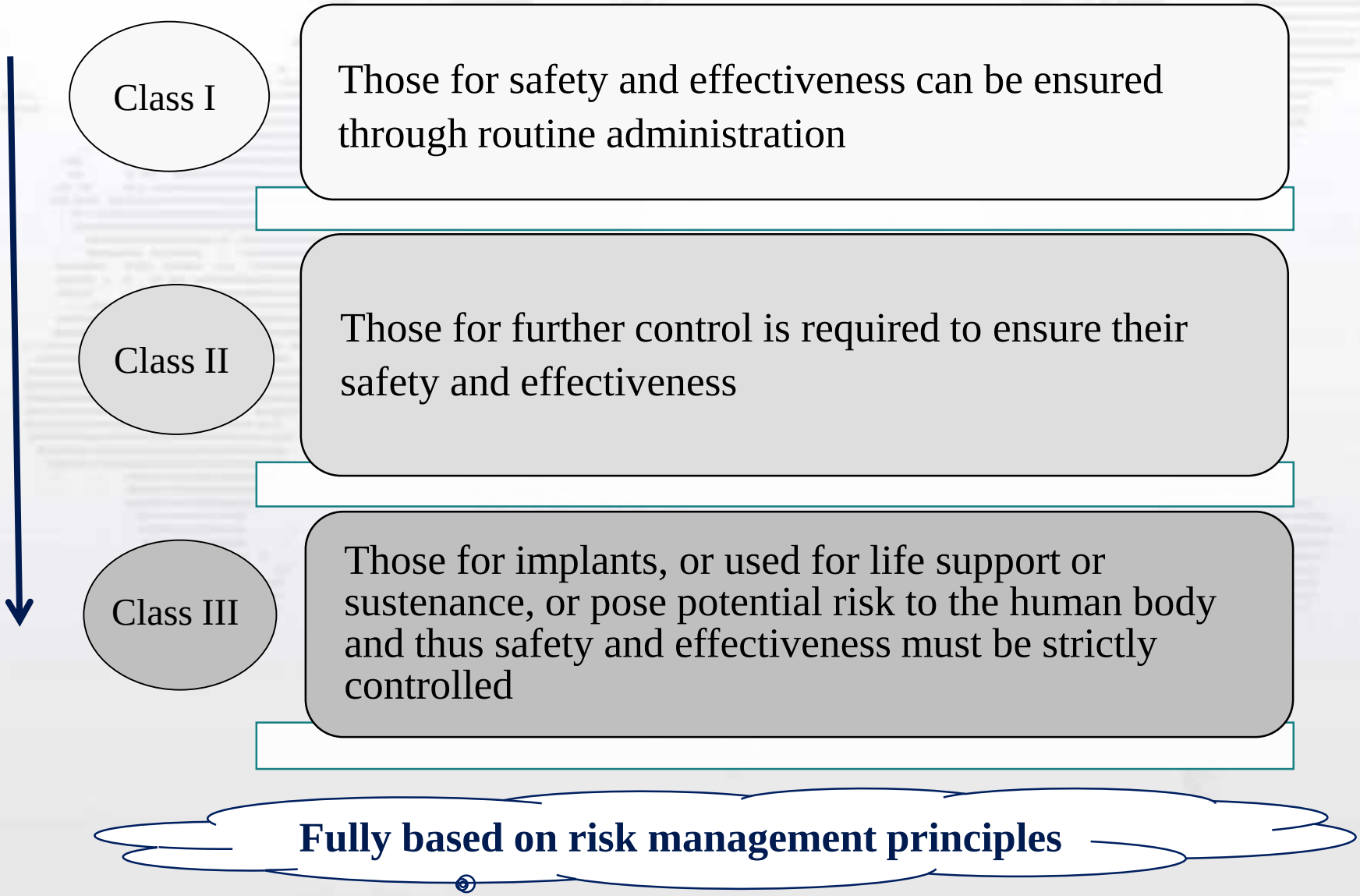
Inspection Centers For Medical Devices

CFDA-Administration Center For Medical Device Standards

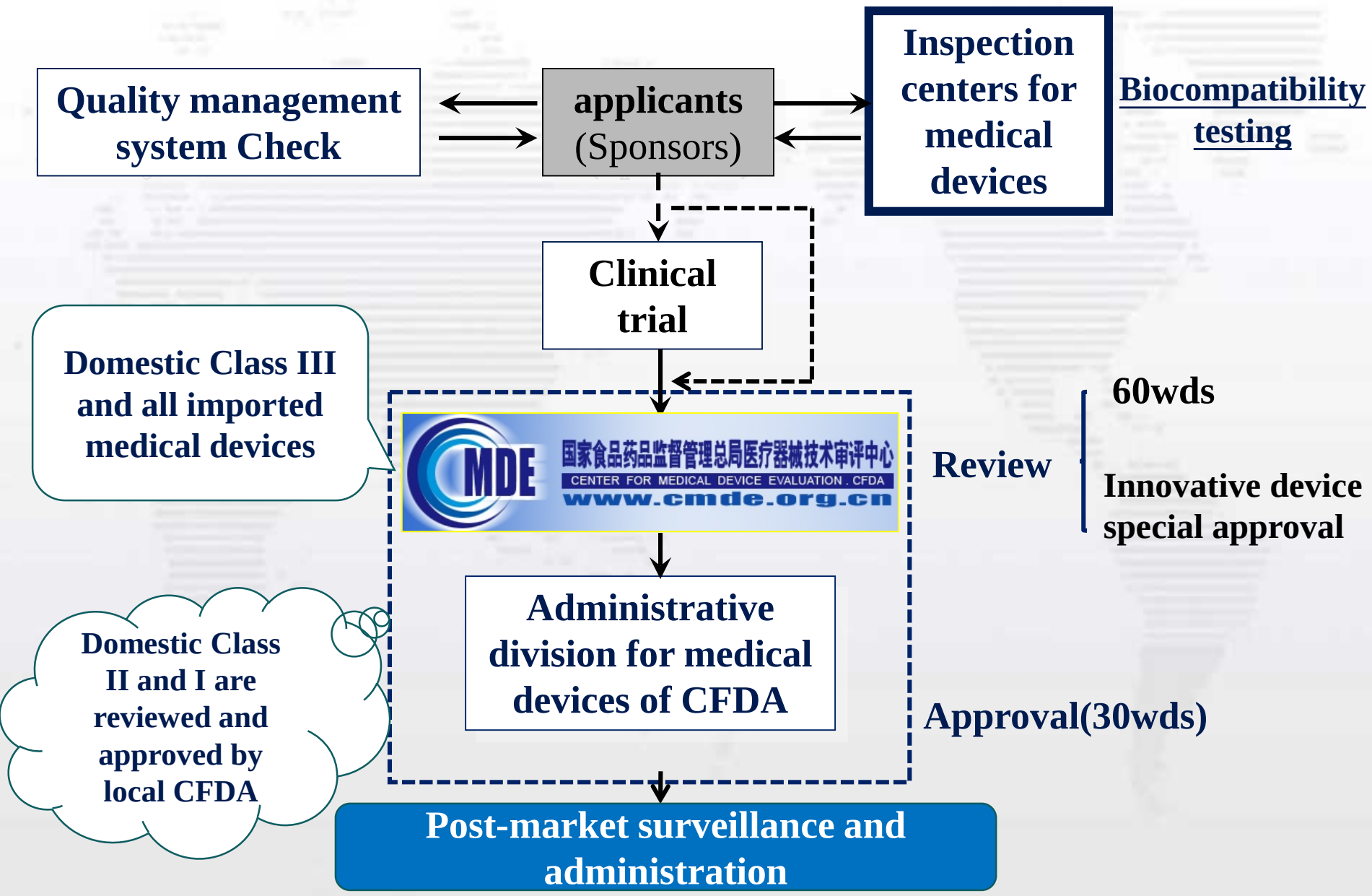
Key Medical Device Regulations

SN	Regulations	Order No.
1	**Regulations on Supervision and Management for medical devices**	**Decree No. 650 the State Council of PRC (2016)**
2	Medical devices registration administration method	No.4 of CFDA(2014)
3	Good clinical practice for clinical trials of medical devices	No.25 of CFDA(2016)
4	Medical device labels and packaging regulations	No.10 of CFDA(2014)
5	Medical devices standard administration method	No.33 of CFDA(2017)
6	Medical devices production, supervision and administration method	No.7 of CFDA(2014)
7	Codes for medical device classification	No.15 of CFDA(2015)
8	Business license to operate medical device management	No.8 of CFDA(2014)
9	Methods for quality system inspection on medical device Good manufacture practice	No.64 of CFDA(2014)
10	Classified catalogue of medical devices	No.104 of CFDA(2017)

Category of Medical devices



Submission and Registration flowchart



Submission and Registration

QMS Check

Methods for quality system inspection on medical device Good manufacture practice VS YY 0287--ISO13485, IDT

Clinical trial

Good clinical practice for clinical trials of medical devices VS ISO14155

So far, CFDA has released hundreds of guidelines for device submission, e.g.

- Hemostatic product guidelines
- Hernia repair mess guidelines
- Medical devices of animal origin
- ……

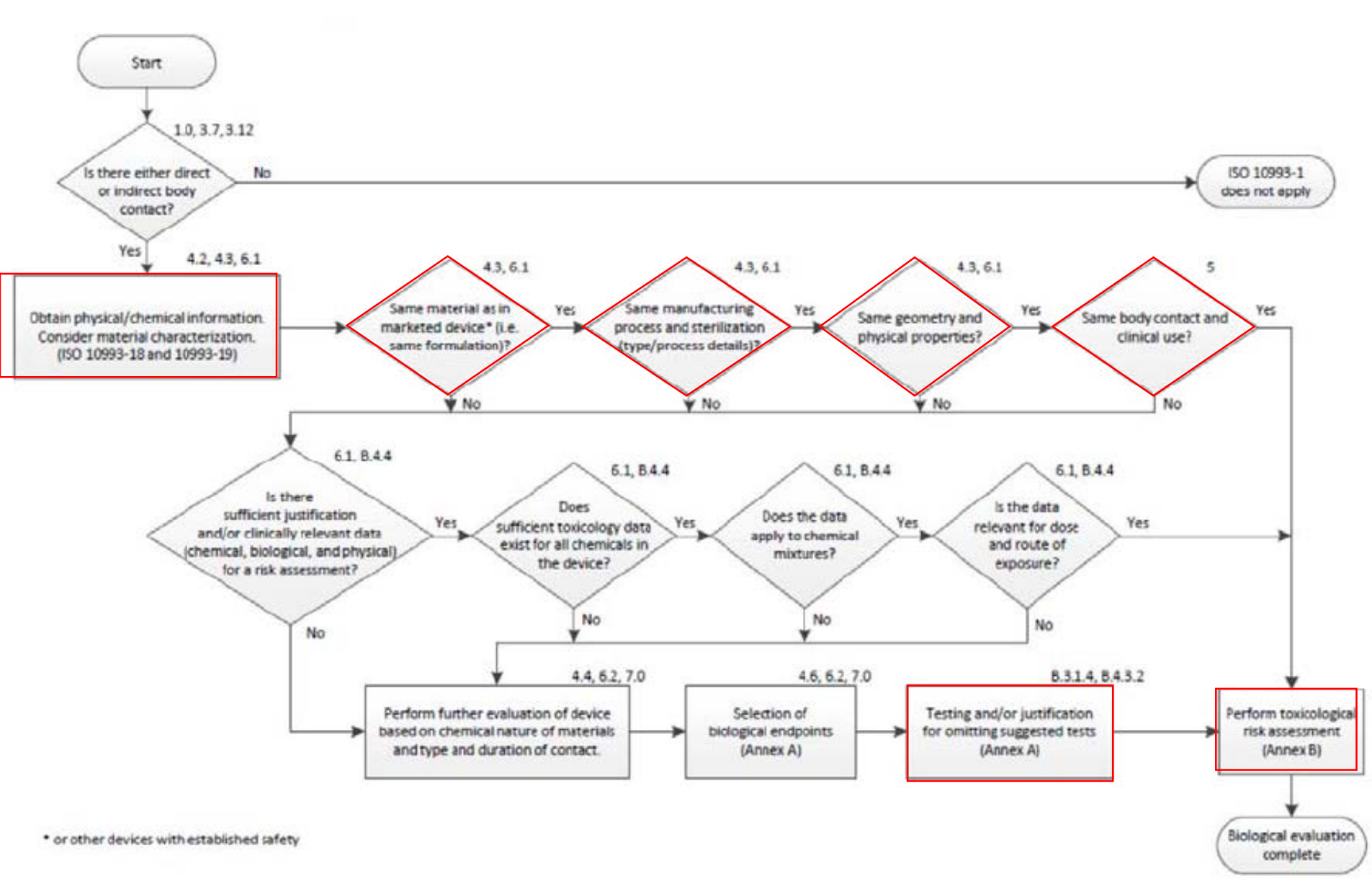
Registration charges for medical devices

(10, 000 U, RMB)

Category		Domestic	Imported
Class II	Initial registration	Based on local government	21.09
	Change of Registration	Based on local government	4.20
	De novo registration(per 5 years)	Based on local government	4.08
Class III	Initial registration	15.36	30.88
	Change of Registration	5.04	5.04
	De novo registration(per 5 years)	4.08	4.08
	Clinical trial application fee(high-risk medical devices)	4.32	4.32

From May 27, 2015

Biological Evaluation overview



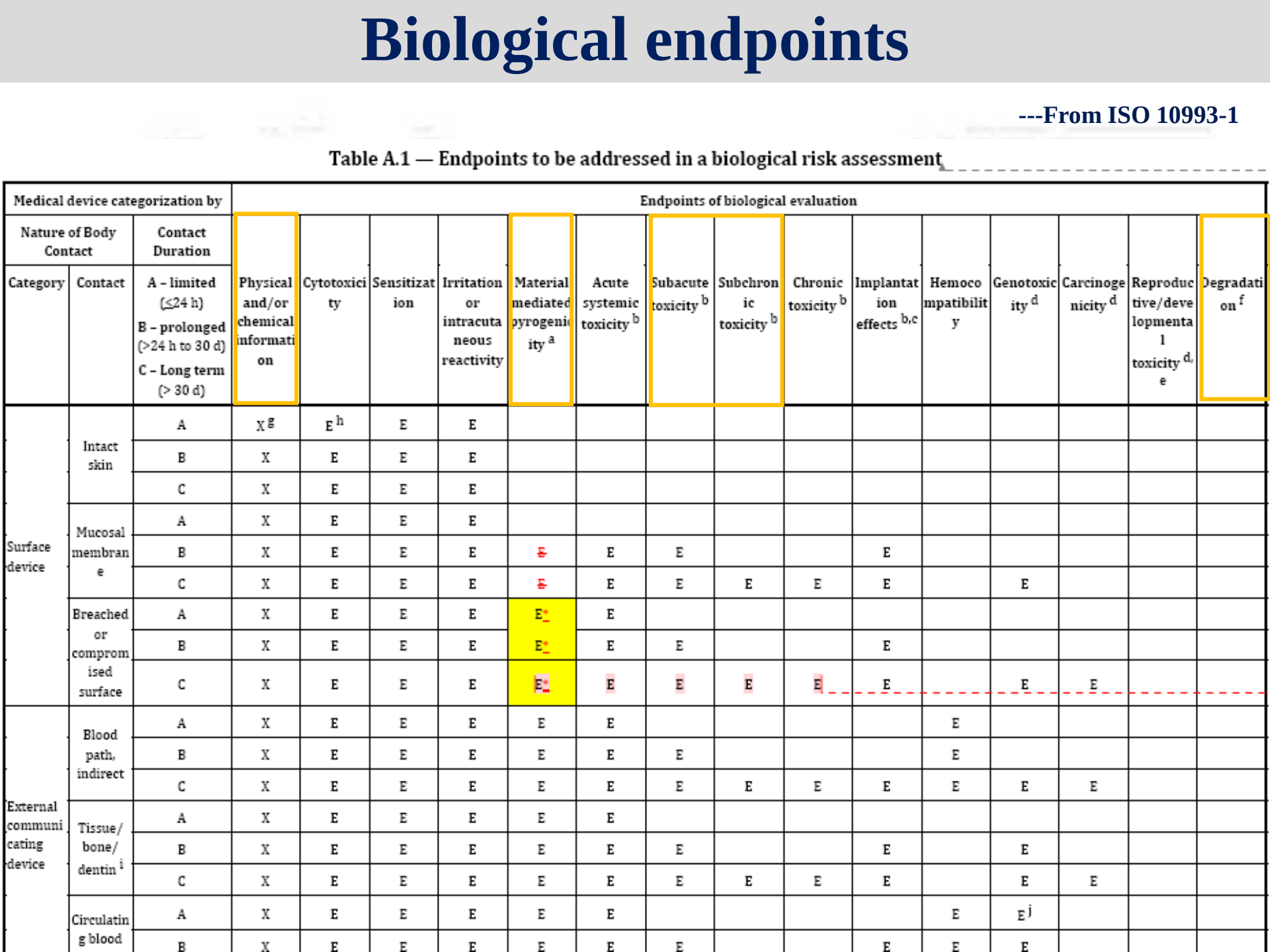
---From ISO 10993-1

Biological endpoints

---From ISO 10993-1

Table A.1 — Endpoints to be addressed in a biological risk assessment

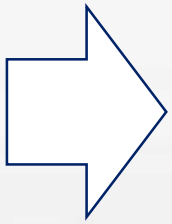
Medical device categorization by			Endpoints of biological evaluation														
Nature of Body Contact		Contact Duration	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity [a]	Acute systemic toxicity [b]	Subacute toxicity [b]	Subchronic toxicity [b]	Chronic toxicity [b]	Implantation effects [b,c]	Hemocompatibility	Genotoxicity [d]	Carcinogenicity [d]	Reproductive/developmental toxicity [d,e]	Degradation [f]
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (> 30 d)															
Surface device	Intact skin	A	X [g]	E [h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E*	E									
		B	X	E	E	E	E*	E	E			E					
		C	X	E	E	E	E*	E	E	E	E	E		E	E		
External communicating device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/bone/dentin [i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E [j]			
		B	X	E	E	E	E	E	E			E	E	E			



Biological Risk Assessment

Biological evaluation shall be initiated from material characterization

Physico-chemical characterization of materials and devices



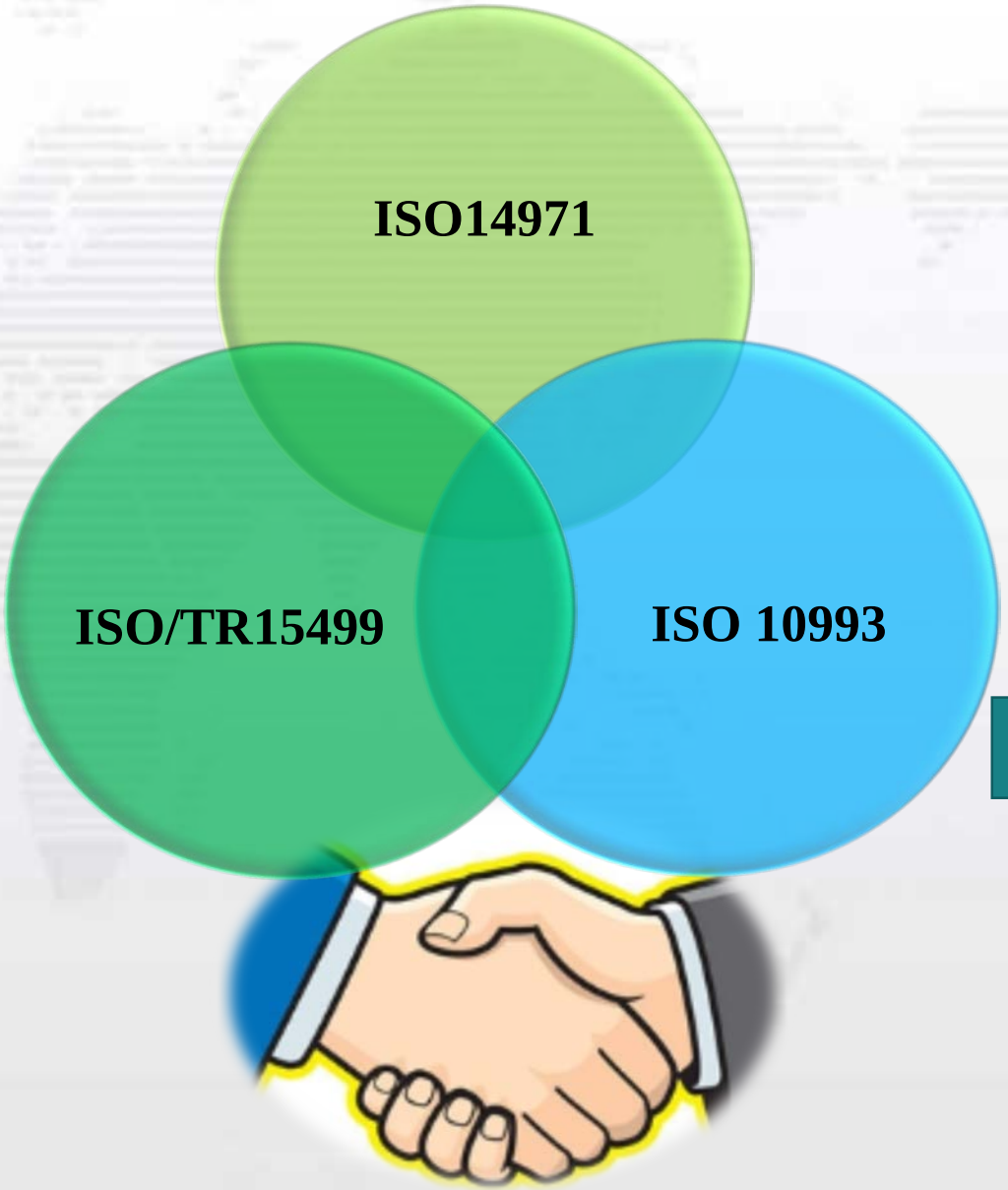
Where applicable, biological tests（in vitro and in vivo）

Toxicological risk assessment

TTC

Threshold of Toxicological Concern(TTC)

Biological Risk Assessment



Evaluation report

Biocompatibility tests

1. Materials and devices that are expected to have direct or indirect contact with the user's body during intended use

2. Biocompatibility test should be performed based on the appropriate standard by CFDA approved inspection center (Physico-chemical tests included)

3. For regulatory submission, test samples should be (or equivalent to)final finished devices ready for the market

4. For extraction, polar & non-polar vehicles are usually used, under the appropriate conditions and ratios, along with E&L consideration

ISO10993 standard series

Biocompatibility tests

- Specific items based on the sponsor’s requirements, usually after pre-submission discussion with review agency
- Biological report from GLP-compliant lab might also be accepted
- Fully based on Toxicological risk assessment
- Focus on endpoint evaluation instead of testing
- Use of physical and chemical characterization and data available in lieu of testing

Biocompatibility tests

CFDA [2007] No.345

① The material suppliers or technical specifications do not change;

② The formulation, process, or primary packaging or sterilization do not change;

③ The final product in the storage period does not change;

④ The intended use does not change;

⑤ There are no indications to cause potential side effects

If all the above provisions are fulfilled, biocompatibility tests should be negligible when re-registration

Biocompatibility Standards in China

ISO 10993-1:2009/Cor 1:2010
ISO 10993-2:2006
ISO 10993-3:2014
ISO 10993-4:2017
ISO 10993-5:2009
ISO 10993-6:2015
ISO 10993-7:2008/Cor 1:2009
ISO 10993-9:2009
ISO 10993-10:2010
ISO 10993-11:2017
ISO 10993-12:2012
ISO 10993-13:2010
ISO 10993-14:2001
ISO 10993-15:2000
ISO 10993-16:2016
ISO 10993-17:2002
ISO 10993-18:2005
ISO/TS 10993-19:2006
ISO/TS 10993-20:2006
ISO/PDTR 10993-55:2016
ISO/TR 10993-33:2015

GB/T16886---ISO10993 IDT

ISO

ISO 13022:2012
ISO 22442-1:2015
ISO 22442-2:2015
ISO 22442-3:2007
ISO/TR 22442-4:2010

ISO/TC194

ISO/TC194/SC1

DIS：1　CD：5　NP：8

➢ISO/DIS 10993-1

- ◆ISO/CD Amd10993-7
- ◆ISO/CD 10993-9
- ◆ISO/CD 10993-15
- ◆ISO/CD 10993-18
- ◆ISO /CD 14155

- ✲ISO /NP TR10993-55
- ✲ISO/NP TS 10993-19
- ✲ISO/NP TS 10993-20
- ✲ISO/DTR 21582
- ✲ISO/NP TS 21726
- ✲ISO/AWI TS 29741
- ✲ISO/NP TS 37137-1
- ✲ISO/DTR 37137-2

Standard development in China

中国国家标准化管理委员会
STANDARDIZATION ADMINISTRATION OF THE PEOPLE'S REPUBLIC OF CHINA

国家食品药品监督管理总局 CFDA
China Food and Drug Administration

- National standards(GB) and industry standards (YY)
- GB are approved and released by Standardization administration of the People's Republic of China(SAC)
- YY are approved and issued by CFDA

222 GB

1243 YY

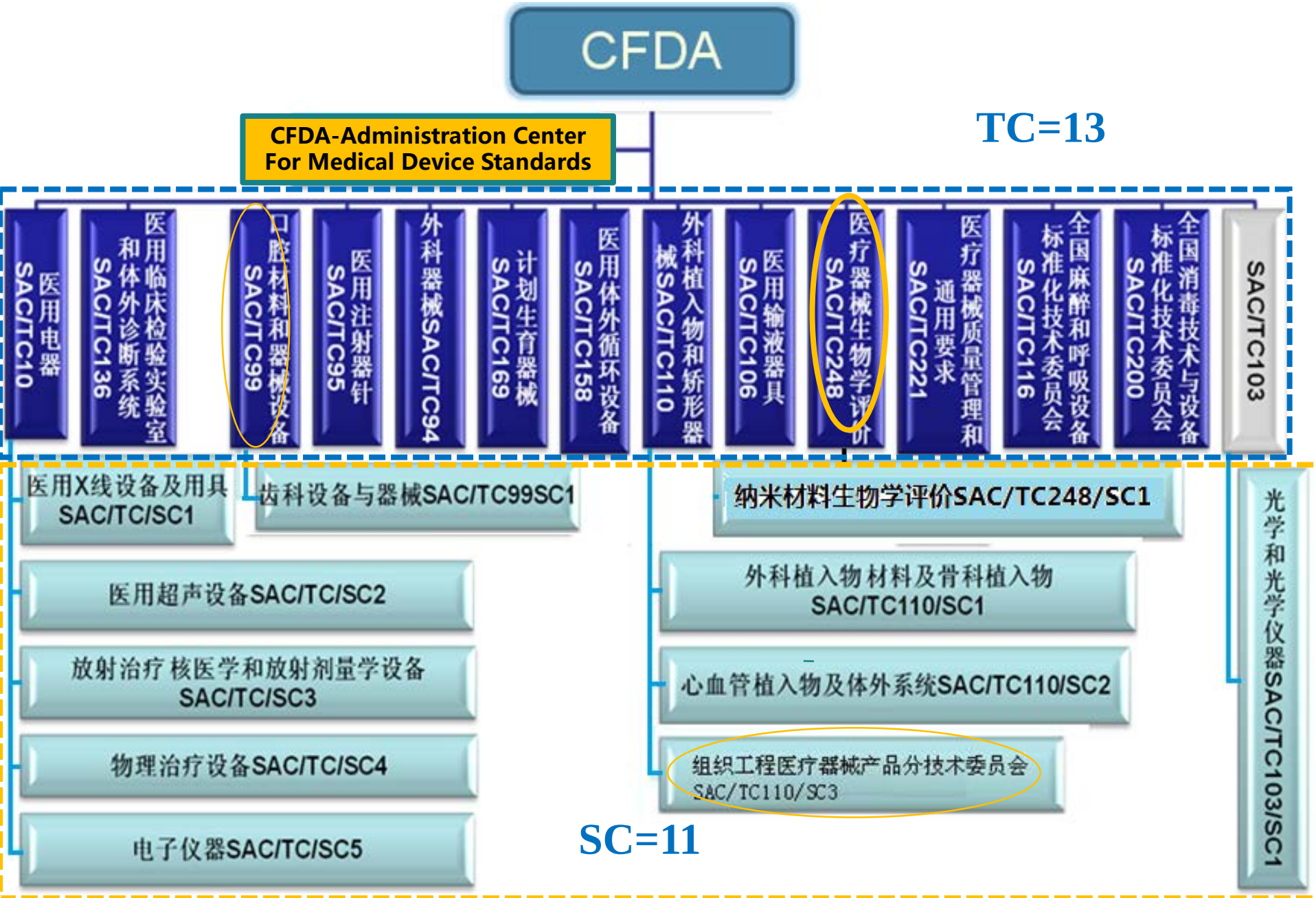
Standard development in China

- YY are totally for medical devices, whereas only a few GB for medical devices
- GB usually involve basic safety or general aspects, e.g. GB/T16886, GB 9706
- YY mostly for specific products or methods to support GB

222 GB

1243 YY

Standard Committees in China



Standard development process in China

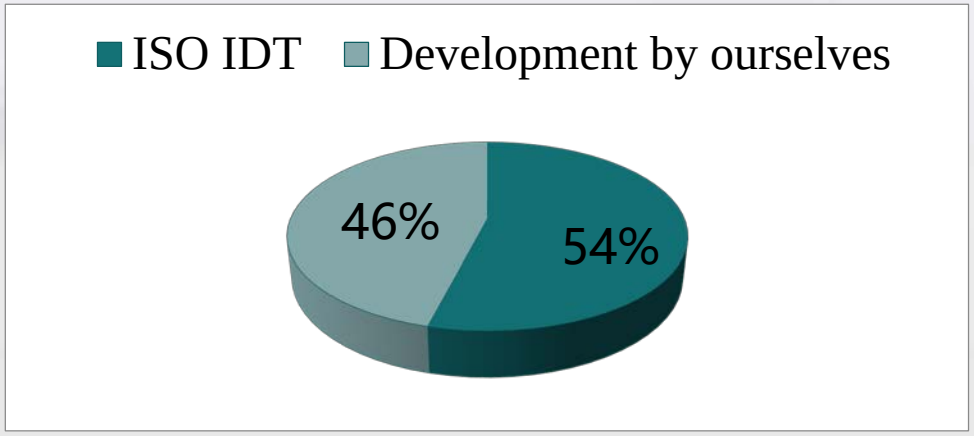
Procedures for standard development

Guarantee the quality of standards

Standards of biological evaluation in China

☑Biological evaluation standards（54/62）

- Principle and general requirement standards（4/4）
- Test and evaluation standards（28/35）
- Degradation test and evaluation standards（7/7）
- Physico-chemical test and evaluation standards（3/3）
- Clinical investigation（2/2）
- Microorganism control（3/3）
- Virus control and safety evaluation for medical device of animal origin（5/6）
- Specific devices (2/2)



Standards of biological evaluation in China

ISO10993 Series, IDT

- ✓ GB/T 16886.1-2011 –ISO10993-1:2009
- ✓ GB/T16886.2-2011—ISO10993-2:2006
- ✓ GB/T16886.3-2008 –ISO10993-3:2003
- ✓ GB/T16886.4-2003--ISO10993-4:2002
- ✓ GB/T16886.5-2017—ISO10993-5:2009
- ✓ GB/T 16886.6-2015—ISO10993-6:2007
- ✓ GB/T 16886.7-2015—ISO10993-7:2008
- × GB/T16886.8-2000
- ✓ GB/T16886.9-2018—ISO10993-9:2009
- ✓ GB/T16886.10-2017—ISO10993-10:2010
- ✓ GB/T16886.11-2011—ISO10993-11:2006
- ✓ GB/T16886.12-2018—ISO10993-12:2012
- ✓ GB/T16886.13-2018—ISO10993-13:2010
- ✓ GB/T16886.14-2003--ISO10993-14:2001
- ✓ GB/T16886.15-2003 --ISO10993-15:2000
- ✓ GB/T16886.16-2013—ISO10993-16:2010
- ✓ GB/T16886.17-2005--ISO10993-17:2002
- ✓ GB/T16886.18-2011--ISO10993-18:2005
- ✓ GB/T16886.19-2011--ISO10993-19:2006
- ✓ GB/T 16886.20-2015--ISO10993-20:2006

Current GB/T16886 supplements

- ✓YY/T 0473-2004
- ✓YY/T 0474-2004
- ✓YY/T 0511-2009
- ✓YY/T 0297-19
- ✓YY/T 0616-2016
- ✓YY/T0870.1-2013
- ✓YY/T0870.2-2013
- ✓YY/T0870.3-2013
- ✓YY 0970-2014
- ✓YY/T0870.4-2014
- ✓YY/T0870.5-2014
- ✓YY/T0879.1-2013
- ✓YY/T0879.2-2015
- ✓YY/T 1500—2016
- ✓YY/T1465.1—2016
- ✓YY/T 1465.2—2016
- ✓YY/T 1465.3—2016
- ✓YY/T 1465.4—2016
- ✓YY/T 1465.5—2016
- ✓YY/T 1512-2017
- ✓YY/T 1292.4-2017
- ✓YY/T 1465.4-2017
- ✓YY/T 0618-2017

Currently 35 released

Practices and Future trends

- Establishment of new biological test methods
  - Use of neo-mode animals
  - In vitro in lieu of in vivo methods
  - Molecular compatibility tests
  - Pre-clinical study using large animals
- Biological evaluation based on risk management
  - Material characterization and toxicological risk estimation
  - Literature review and risk assessment
  - Risk management and biological evaluation

CFDA-Jinan Inspection Center

- Jinan center is one of the ten inspection centers for medical devices accredited by CFDA and CNAS(ilac)
- **Fully ISO/IEC 17025 Accreditated**

ISO/IEC 17025

Base on reference standards and validated methods

VS.

GLP

Base on case by case Protocols

Quality and integrity of the data

58 testing centers, 10 affiliated to CFDA

CFDA-Jinan Inspection Center

FACILITIES

- 26,000m^2 functional building
- 3500m^2 animal facility for on-site monitoring and housing
- 10 plus divisions involved in biological, chemical, physical and varieties of testing items
- Fully ISO/IEC 17025 accreditated

PERSONNEL

- 200 full-time staffs
- Most staffs have high academic backgrounds and rich experience
- CFDA Pre-market audit experts
- QAU

CFDA-Jinan Inspection Center

- To date, with 800 plus product originated inspection ability. Responsible for technical interpretation for biological evaluation of biomaterials and medical devices in China
- The largest animal center for biological evaluation in China
- China secretariats of Biological evaluation(ISO/TC194) and Infusion Equipment for Medical Use (ISO/TC76)
- Key lab for biological evaluation of medical devices in China

Shandong Quality Inspection Center For Medical Devices （CFDA-Jinan center）

◆ Safety evaluation for variables of new materials and devices（ Physico-chemical and biological evaluation ）, pre-clinical study（efficacy test）, Aim to offer you the best solutions!

Key competence

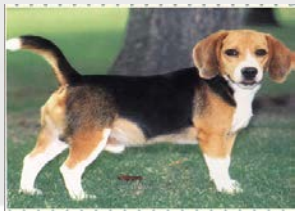
Whole life-cycle quality evaluation!

1. Physico-chemical characterization
2. Biological evaluation（ Safety and Efficacy ）
3. Microorganism performance evaluation（ Resistance to microbial penetration and anti-microorganism ）









THANK YOU!

山东省医疗器械产品质量检验中心