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

Chenghu Liu

October 13, 2017

Tel: +86 531-82682901
Cell: +86 15688896811
E-mail: liuchenghu510@163.com
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

- Local Government CFDA
  - Local Government CFDA Review Centers
    - Inspection Centers For Medical Devices
      - CFDA-Administration Center For Medical Device Standards

Administrative and regulatory agency

Technical support
<table>
<thead>
<tr>
<th>SN</th>
<th>Regulations</th>
<th>Order No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Regulations on Supervision and Management for medical devices</td>
<td>Decree No. 650 the State Council of PRC (2016)</td>
</tr>
<tr>
<td>2</td>
<td>Medical devices registration administration method</td>
<td>No.4 of CFDA(2014)</td>
</tr>
<tr>
<td>3</td>
<td>Good clinical practice for clinical trials of medical devices</td>
<td>No.25 of CFDA(2016)</td>
</tr>
<tr>
<td>4</td>
<td>Medical device labels and packaging regulations</td>
<td>No.10 of CFDA(2014)</td>
</tr>
<tr>
<td>5</td>
<td>Medical devices standard administration method</td>
<td>No.33 of CFDA(2017)</td>
</tr>
<tr>
<td>6</td>
<td>Medical devices production, supervision and administration method</td>
<td>No.7 of CFDA(2014)</td>
</tr>
<tr>
<td>7</td>
<td>Codes for medical device classification</td>
<td>No.15 of CFDA(2015)</td>
</tr>
<tr>
<td>8</td>
<td>Business license to operate medical device management</td>
<td>No.8 of CFDA(2014)</td>
</tr>
<tr>
<td>9</td>
<td>Methods for quality system inspection on medical device Good manufacture practice</td>
<td>No.64 of CFDA(2014)</td>
</tr>
<tr>
<td>10</td>
<td>Classified catalogue of medical devices</td>
<td>No.104 of CFDA(2017)</td>
</tr>
</tbody>
</table>
Those for safety and effectiveness can be ensured through routine administration.

Those for further control is required to ensure their safety and effectiveness.

Those for implants, or used for life support or sustenance, or pose potential risk to the human body and thus safety and effectiveness must be strictly controlled.

Category of Medical devices

Class I

Class II

Class III

Fully based on risk management principles
Submission and Registration flowchart

Quality management system Check

applicants (Sponsors)

Inspection centers for medical devices

Clinical trial

Biocompatibility testing

Domestic Class III and all imported medical devices

Domestic Class II and I are reviewed and approved by local CFDA

Administrative division for medical devices of CFDA

Review

60wds

Innovative device special approval

Approval (30wds)

Post-market surveillance and administration
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
◆ ……
<table>
<thead>
<tr>
<th>Category</th>
<th>Domestic</th>
<th>Imported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial registration</td>
<td>Based on local government</td>
<td>21.09</td>
</tr>
<tr>
<td>Change of Registration</td>
<td>Based on local government</td>
<td>4.20</td>
</tr>
<tr>
<td>De novo registration (per 5 years)</td>
<td>Based on local government</td>
<td>4.08</td>
</tr>
<tr>
<td>Class III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial registration</td>
<td>15.36</td>
<td>30.88</td>
</tr>
<tr>
<td>Change of Registration</td>
<td>5.04</td>
<td>5.04</td>
</tr>
<tr>
<td>De novo registration (per 5 years)</td>
<td>4.08</td>
<td>4.08</td>
</tr>
<tr>
<td>Clinical trial application fee</td>
<td>4.32</td>
<td>4.32</td>
</tr>
</tbody>
</table>

From May 27, 2015
Biological Evaluation overview

---From ISO 10993-1

* or other devices with established safety
## Biological endpoints

---From ISO 10993-1

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

<table>
<thead>
<tr>
<th>Medical device categorization by</th>
<th>Contact Duration</th>
<th>Physical and/or chemical information</th>
<th>Cytotoxicity</th>
<th>Sensitization</th>
<th>Irritation or intracutaneous reactivity</th>
<th>Material mediated pyrogenicity</th>
<th>Acute systemic toxicity</th>
<th>Subacute toxicity</th>
<th>Subchronic toxicity</th>
<th>Chronic toxicity</th>
<th>Implantation effects</th>
<th>Hemocompatibility</th>
<th>Genotoxicity</th>
<th>Carcinogenicity</th>
<th>Reproductive/developmental toxicity</th>
<th>Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface device</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact skin</td>
<td>A</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal membrane</td>
<td>A</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breached or compromised surface</td>
<td>A</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood path. indirect</td>
<td>A</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External communicating device</td>
<td>Tissue/bone/dentin</td>
<td>A</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulating blood</td>
<td>A</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>×</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---From ISO 10993-1
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.

Threshold of Toxicological Concern (TTC).
Biological Risk Assessment

ISO14971

ISO/TR15499

ISO 10993

Evaluation report
<table>
<thead>
<tr>
<th><strong>Biocompatibility tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Materials and devices that are expected to have direct or indirect contact with the user’s body during intended use</td>
</tr>
<tr>
<td><strong>2</strong> Biocompatibility test should be performed based on the appropriate standard by CFDA approved inspection center (Physico-chemical tests included)</td>
</tr>
<tr>
<td><strong>3</strong> For regulatory submission, test samples should be (or equivalent to) final finished devices ready for the market</td>
</tr>
<tr>
<td><strong>4</strong> For extraction, polar &amp; non-polar vehicles are usually used, under the appropriate conditions and ratios, along with E&amp;L consideration</td>
</tr>
</tbody>
</table>
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

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.

CFDA [2007] No.345
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 10993-20:2006
ISO/TR 10993-33:2015

ISO/CD 10993-1
ISO/CD Amd 10993-7
ISO/CD 10993-9
ISO/CD 10993-15
ISO/CD 10993-18
ISO/CD 14155

GB/T 16886—ISO 10993 IDT
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
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
Standard Committees in China

CFDA-Administration Center
For Medical Device Standards

TC=13

SC=11
Procedures for standard development

To achieve the whole process management

Guarantee the quality of standards
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)

ISO IDT: 46%
Development by ourselves: 54%
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
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

GLP
Base on case by case Protocols

58 testing centers, 10 affiliated to CFDA
CFDA-Jinan Inspection Center

FACILITIES
- 26,000m² functional building
- 3500m² 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 accredited

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

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