Regulations on In-Vitro Diagnostic Devices

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Outlines

- Medical Device Regulatory Framework
- In Vitro Diagnostic Medical Device
  - Pre-Market Approval Processes
  - Technical Documents
  - Reference and Database
Medical Device Regulatory Framework
Medical Device Regulatory Framework

- Beginning of registration: 1973
- GMP implementation: 1999
- Reclassification: 2000
- No. of registered MD licenses: 45,890 (as of 2018)
- No. of registered MD manufactures: 1,582 (as of 2018)
Medical Device Life Cycle Management

Medical Care Needs/ Fundamental Study → Product Design/ Prototype Development → Preclinical Validation → Clinical Trial → Premarket Application → Production → Post-market Surveillance

- General/Case Consultation
- Laboratory Practices (GLP/GTP)
- Clinical Trial Inspection (GCP)
- Clinical Trial Protocol Review (TFDA/IRB)
- Registration (Approval/Listing)
- MD Advisory Committee

Production Quality System Control

- MDs: Medical Devices
- GLP: Good Laboratory Practice
- GTP: Good Tissue Practice
- GCP: Good Clinical Practice
- IRB: Institutional Review Board
- GMP: Good Manufacturing Practice
- ADR: Adverse Drug/Device Reaction
- GVP: Good Vigilance Practice

MD Advisory Committee

Manufacturer’s Quality System Audit (GMP)

- ADR & Product Defect Reporting
- Safety Surveillance & Alert Collection (GVP)
- Consumer Health Education Promotion
- Good Distribution Practice (GDP)
Basis of Medical Device Regulation

Pharmaceutical Affairs Act
Medical Care Act

Regulations for Governing the Management of MD
- Regulation for Registration of MD
- Good Manufacturing Practice Regulations (GMP)
- Good Clinical Practice (GCP)
- Good Laboratory Practice (GLP)
- Regulations for Drug Safety Monitoring

Guidelines for Registration of In Vitro Diagnostic Medical Device
- Guideline for Additive Manufactured Medical Devices
- Recognized International standards
Medical Device Category

- Pursuant to Article 3 of 《Regulations for Governing the Management of Medical Device》, medical devices classified by intended use and mode of action with seventeen categories.

<table>
<thead>
<tr>
<th>Medical Device Category</th>
<th>Risk Level</th>
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<tbody>
<tr>
<td>Clinical chemistry and clinical toxicology devices</td>
<td>Unclassified</td>
</tr>
<tr>
<td>Hematology and pathology devices</td>
<td>CLASS I</td>
</tr>
<tr>
<td>Immunology and microbiology devices</td>
<td>CLASS II</td>
</tr>
<tr>
<td>Anesthesiology devices</td>
<td>CLASS III</td>
</tr>
<tr>
<td>Cardiovascular devices</td>
<td>LOW RISK</td>
</tr>
<tr>
<td>Dental devices</td>
<td>Medium RISK</td>
</tr>
<tr>
<td>Ear, nose, and throat devices</td>
<td>HIGH RISK</td>
</tr>
<tr>
<td>Gastroenterology devices</td>
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<tr>
<td>General and plastic surgery devices</td>
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<tr>
<td>General hospital and personal use device</td>
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<tr>
<td>Neurological devices</td>
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<tr>
<td>Obstetrical and gynecological devices</td>
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<tr>
<td>Ophthalmic devices</td>
<td></td>
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<tr>
<td>Orthopedic devices</td>
<td></td>
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<tr>
<td>Physical medicine devices</td>
<td></td>
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<tr>
<td>Radiology devices</td>
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</tr>
</tbody>
</table>

Seventeen categories

According to the degree of risk points three levels
In Vitro Diagnostic Medical Device

Pre-Market Approval Processes
Definition of In Vitro Diagnostic Medical Devices

- Regulation for Registration of Medical Devices: (Article 9)

In Vitro Diagnostic Device (hereafter referred to as IVD) referred to in this Regulation is a medical device such as diagnostic reagents, instruments or systems used to collect, prepare, and test specimens from human body in order to diagnose disease or other conditions (including a determination of the state of health).
Marketing an IVD Medical Device Product in Taiwan (1)

- Manufacturing Facility GMP/QSD Application
- Product License Application

DAO: Designated Auditing Organization

DAO Auditing → TFDA

TFDA → Review Center (Document Review)

TFDA Class I / II / III

GMP/QSD Compliance Letter

Testing (HAV, HBV, HCV, HTLV, HIV, ABO…)

Medical Device Advisory Committee (new devices)

Approval → License Granting
Marketing an IVD Medical Device Product in Taiwan (2)

Class I - IVD Submission

Mail

Pay for the registration fee

On-site Registration

Internet registration (under construction)

License

TFDA
Marketing an IVD Medical Device Product in Taiwan (3)

Class II/III - IVD Submission

- Submission
  - Initial-Screening
    - 10 Days
    - Incomplete documents
      - Rejection
      - Re-Screening
  - Complete Initial-Screening
    - Document Review
      - Incomplete documents
        - Correction
          - Two months
        - Disapproval
          - Re-Examination
            - Disapproval
        - Documents fulfilled
          - Approval
            - License Granting
  - Incomplete documents
    - Documents fulfilled*

In Vitro Diagnostic Medical Device

Technical Documents
Active Ingredient information: These descriptions may include, but are not limited to, any of the following: chemical structure, primary and subunit structure, molecular weight, molecular formula, name, antibody class/subclass, etc., as appropriate. Results of all characterization analytical testing shall be submitted, including information on identity, potency, specificity, purity, stability, consistency, etc.
quality control

- Manufacturing process:
  ① Active ingredient manufacturing process: Animal Sources, Human Sources, Cellular Sources, Synthetic Sources
  ② A representation and description of the manufacturing process flow
  ③ Key Process Validation: A description and the results of the process validation studies shall be submitted. purification processes, inactivating or removing any infectious pathogens, potency adjustments…etc. (or 3 Batch Production Records)
Pre-Market Approval Technical Documents for IVD (3)

quality control

- Reference standards/panels:
  1. International Reference Standard: the characterization, specifications and test report of the standards shall be provided
  2. In-house working reference standards: the preparation, characterization, specifications, testing, substitutions, and results shall be provided
Pre-Market Approval Technical Documents for IVD (4)

Pre-clinical test

- According to …
  ① Original manufacturer’s specification
  ② International Standards (eg. CNS、ISO、CLSI、EN、ASTM、IEC… etc.)
  ③ Review Standards（eg. FDA guidance、TFDA guidance… etc.）
  ④ Special claim in label
### Pre-Market Approval Technical Documents for IVD (5)

#### Pre-clinical test

<table>
<thead>
<tr>
<th>Performance characterization</th>
<th>Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision/Reproducibility</td>
<td>CLSI EP5-A2</td>
</tr>
<tr>
<td>Analytical sensitivity</td>
<td>CLSI EP12-A</td>
</tr>
<tr>
<td>Limit of detection, LOD</td>
<td>CLSI EP12-A</td>
</tr>
<tr>
<td>Limit of quantification, LOQ</td>
<td>CLSI EP17-A</td>
</tr>
<tr>
<td>Linearity and measuring range</td>
<td>CLSI EP6-A</td>
</tr>
<tr>
<td>Assay cut-off</td>
<td>CLSI EP24-A2</td>
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<tr>
<td>Analytical specificity</td>
<td>CLSI EP7-A2</td>
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<tr>
<td>Traceability</td>
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</tr>
<tr>
<td>Stability</td>
<td>ISO 23640:2011</td>
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</table>
Pre-Market Approval Technical Documents for IVD (6)

Pre-clinical test

- Specimen:
  1. The type of specimen(s) required (e.g. serum, plasma, whole blood, tissue biopsy, urine)
  2. Testing population
  3. Specimen storage condition
Pre-clinical test

- Similar product available for comparison testing:
  - Pre-clinical performance evaluation may be carried out in direct comparison with a device, which is currently marketed in Taiwan or one of the following countries or areas: United States, Japan, Canada, Switzerland, Australia, or European Union. If there is no similar product available for comparison testing, the following alternatives can be used in order:
    ① Conduct the comparison testing with the reference method
    ② Comply with the recognized standards or other international standards
    ③ Use a widely accepted industrial testing method
Pre-Market Approval Technical Documents for IVD (8)

Clinical Evaluation

- Class III In Vitro Diagnostic Device (IVD)

- New In Vitro Diagnostic Device (IVD)
Pre-Market Approval Technical Documents for IVD (9)

Clinical Evaluation

- Information on the product clinical evaluation, e.g. reproducibility, sensitivity, specificity, cross reactivity shall be submitted for review.

- Positive specimens used in the performance evaluation shall be selected to reflect different stages of the respective disease(s), different antibody patterns, different genotypes, different subtypes, etc.
Clinical evaluation performed domestically

- Beside the submission of performance evaluation information, tests for **HBV, HCV and new IVD** that is used in **screening of blood donors**, the clinical evaluation conduct domestically.
  
  - Clinical evaluation can be conducted after the approval of IRB of the evaluation institutions.
  
  - After reviewing the clinical evaluation report, TFDA can request for clinical evaluation conducted domestically for IVD performance that can have racial or geographical variance.
Reference and Database
Guidelines for Registration of In Vitro Diagnostic Medical Device


## Scope & Definition
Medical Device Management Framework and Glossary

## Product Registration

### Law & Regulations

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
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<tbody>
<tr>
<td>1</td>
<td>Pharmaceutical Affairs Act</td>
<td>2018-10-22</td>
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<td>2</td>
<td>Pharmaceutical Affairs Act Enforcement Rules</td>
<td>2018-10-21</td>
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<tr>
<td>3</td>
<td>Regulations for Governing the Management of Medical Device</td>
<td>2018-10-20</td>
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<td>4</td>
<td>Regulations for Registration of Medical Device</td>
<td>2018-10-19</td>
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<td>5</td>
<td>Guidelines for Registration of In Vitro Diagnostic Medical Device</td>
<td>2018-10-18</td>
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<td>6</td>
<td>Standards of Review Fees for the Registration of Western Medicines and Medical Devices</td>
<td>2018-10-17</td>
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<td>7</td>
<td>Regulations for Approval of Specific Medical Products' Manufacturing or Importing as a Special Case</td>
<td>2018-10-16</td>
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<tr>
<td>8</td>
<td>Regulations on Management of Medicament Samples and Gifts</td>
<td>2018-10-15</td>
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MD Guidance Database (1)

MD Guidance Database (2)

Thank you for your attention!