DCVMN Training Workshop- Global registration and supply shortages
Session: Registration of vaccines and collaboration

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Section Chief, Division of Medicinal Products, Taiwan Food and Drug Administration (TFDA)
Outline

- Organization and Responsibility of TFDA
- Current Regulatory Framework
- Application and Evaluation Process
- Points to Consider on Vaccine (Case Study)
- Future Prospects
Establishment of TFDA

2010

2010.01.01 TFDA Inauguration (食品藥物管理局)
Integration of 4 bureaus:
• Food Safety (食品處)
• Pharmaceutical Affairs (藥政處)
• Food & Drug Analysis (食品藥物檢驗局)
• Controlled Drugs (管制藥品管理局)

2013

2013.07.23 TFDA Elevation (食品藥物管理署)
The Ministry of Health and Welfare (MOHW) was restructured from the Department of Health (DOH).
The Role of TFDA

Protect
Assure Quality, Safety, Efficacy of Medicinal Products

Promote
Facilitate the Development of Innovative Medicine and Speed Drug Accessibility
CDE is a nongovernmental organization commissioned by the TFDA to evaluate technical dossiers of IND and NDA application
Total license: 24,978

Taiwan Market
- Population: 23 millions
- 160~240 thousand newborn babies/yr
- 16~18 million doses/yr released by TFDA
- 11 million doses/yr for EPI
## Licensed Vaccines in Taiwan

<table>
<thead>
<tr>
<th><strong>Approved Vaccine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domestic</strong></td>
</tr>
<tr>
<td>• Bacille Calmette-Guerin vaccine (BCG)</td>
</tr>
<tr>
<td>• Mouse brain-derived JE vaccine</td>
</tr>
<tr>
<td>• Seasonal flu vaccine</td>
</tr>
<tr>
<td>• Tetanus toxoid</td>
</tr>
<tr>
<td><strong>Import</strong></td>
</tr>
<tr>
<td>• Hepatitis B vaccine (HepB)</td>
</tr>
<tr>
<td>• DTaP-Hib-IPV 5 in 1</td>
</tr>
<tr>
<td>• DTaP</td>
</tr>
<tr>
<td>• Inactivated polio vaccine (IPV)</td>
</tr>
<tr>
<td>• Pneumococcal vaccine (PV)</td>
</tr>
<tr>
<td>• Varicella vaccine (Varicella)</td>
</tr>
<tr>
<td>• Measles, mumps and rubella vaccine (MMR)</td>
</tr>
<tr>
<td>• Cell -based JE vaccine</td>
</tr>
<tr>
<td>• Seasonal flu vaccine</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Vaccinations for The Expanded Program on Immunization (EPI)</strong></th>
</tr>
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<tbody>
<tr>
<td>• Rotavirus vaccine (Rotavirus)</td>
</tr>
<tr>
<td>• Hepatitis A vaccine (HepA)</td>
</tr>
<tr>
<td>• DTaP-IPV-HepB-Hib 6 in 1</td>
</tr>
<tr>
<td>• DTap-IPV 4 in 1</td>
</tr>
<tr>
<td>• Rabies vaccine (Rabies)</td>
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</tbody>
</table>

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<thead>
<tr>
<th><strong>Others</strong></th>
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</thead>
<tbody>
<tr>
<td>• Human Papillomavirus vaccine Type 16 and 18</td>
</tr>
<tr>
<td>• Quadrivalent Human Papillomavirus (Types 6,11,16,18)</td>
</tr>
<tr>
<td>• Human Papillomavirus 9-valent Vaccine, Recombinant</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HPV Vaccine</strong></th>
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<tr>
<td>• Typhoid fever vaccine (Typhoid)</td>
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<tr>
<td>• Yellow fever vaccine (YF)</td>
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<tr>
<td>• Meningococcal C conjugate vaccine (Men C_conj)</td>
</tr>
<tr>
<td>• Others (Vaccines in Delay or Shortage)</td>
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<tr>
<th><strong>Specific Import by CDC</strong></th>
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Outline

- Organization and Responsibility of TFDA
- **Current Regulatory Framework**
- Application and Evaluation Process
- Points to Consider on Vaccine (Case Study)
- Future Prospects
Life Cycle Management

Basic Research → Product Development → Pre-clinical Studies → IND Clinical Trial → NDA Market licensing → Production → Postmarket Surveillance

**Pre-Market Approval**
- GLP: Good Laboratory Practice
- GCP: Good Clinical Practice
- IRB: Institutional Review Board
- SUSAR: Suspected Unexpected Serious Adverse Reactions
- GMP: Good Manufacturing Practice
- ADR: Adverse Drug/Device Reaction
- GPvP: Good Pharmacovigilance Practices
- GDP: Good Distribution Practice
- GVP: Good Vigilance Practice
- GPP: Good Pharmacy Practice
- RMP: Risk management plan

**Lot release:** Each lot must be tested for purity, potency, identity, and sterility

**Post-Market Control**
- Supplement (post-licensure changes, i.e., new indication or facility...)
- GDP
- GPvP
- GPP
- ADR & Product Defect Reporting
- Drug injury relief
- RMP

**PICS/GMP**

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Pre-clinical Studies → IND Clinical Trial → NDA Market licensing → Production → Postmarket Surveillance

- Basic Research
- Product Development
- Pre-clinical Studies
- IND Clinical Trial
- NDA Market licensing
- Production
- Postmarket Surveillance

- Consultation
- IRB
- SUSAR Reporting
- Lot release
- Supplement (post-licensure changes, i.e., new indication or facility...)
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Optimize Regulations for Quality

- PIC/S Participating Authority since 2013
- All manufacturers shall fully comply with the current version of PIC/S GMP Guide since 2015
- Current status: (up to 23 February 2017)
  - Domestic pharmaceutical manufacturers: 130
  - Companies not comply with PIC/S GMP
    - *shall cease manufacturing and be delisted.*
# Legislation and Regulation

## Legislation and Regulations on Vaccine

<table>
<thead>
<tr>
<th>Law</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Affairs Act</td>
<td>Regulation for Registration of Medicinal Products</td>
</tr>
<tr>
<td>Medical Care Act</td>
<td>Regulations on Human Trials</td>
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<tr>
<td></td>
<td>Regulation on Good Clinical Practice (GCP)</td>
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<td></td>
<td>Regulation on Good Manufacture Practice (GMP)</td>
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<tr>
<td></td>
<td>Regulation of the Lot Release Procedures for Biologics</td>
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<table>
<thead>
<tr>
<th>Guidance</th>
<th>Regulation for Registration of Vaccines</th>
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<tbody>
<tr>
<td></td>
<td>Guidance for Registration of Pandemic Influenza Vaccines</td>
</tr>
<tr>
<td></td>
<td>Guidance for Strain Change Supplements of Seasonal Flu Vaccines</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>International Guidance</th>
<th>ICH/EMA/FDA/WHO guidance which are issued in an issue-specific manner are taken into reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E.g., viral safety, expression construct, specification, cell substrate, individual vaccine</td>
</tr>
</tbody>
</table>
Approval of Specific Drugs

When a special case happened in the following circumstances..........

1. For the **life-threatening, severely disability diseases**
   - **No** appropriate drug or alternative treatment

2. In responding to the necessity of **emergency public health** circumstances (**Emergency Use Authorization, EUA**)

TFDA can **approve to manufacture and import** the specific drugs that are not licensed in Taiwan, ex. Yellow Fever Vaccine (YF).
Ensuring sufficiency in Drugs

§ 27-2

Government:
- establishing the on-line reporting platform
- Announcing essential drug list and regulations

Stakeholders:
- For essential drugs, stakeholders should notify the authority 6 months ahead for possible supply inadequacy due to manufacturing, importation or others issues.

Prevention
- on-line reporting platform
- essential drugs list

Reporting & Evaluation
- Event reporting
- Evaluation for possible substitution

Action
- dispatch
- Special permit in manufacturing and importation for essential drugs
Enhance Drug Supply Chain Integrity

- **Government:**
  - Announcing drug items to be traced and reported
  - Establishing e-reporting system
- **Stakeholders:**
  - Establishing traceability system and e-reporting
Implement Good Distribution Practice

Manufacture

- GMP
  Good Manufacturing Practices

Storage, Transportation

- GDP
  Good Distribution Practices

Ensuring the quality and package integrity during the manufacturing, storage and transportation.

Hospital, Pharmacy to Patients

- GDP
  Good Dispensing Practices

Quality Assurance
Implementation Schedule of GDP

Announcement of “Guide to Good Distribution Practice for Medicinal Products” 【2015-7-16】

NEW

From July 1, 2016, all new manufacturer, logistics company and license applicator shall comply

ALL

By January 1, 2019, the existed manufacturers, logistics companies and license holder shall comply

Inspection: with GMP, or application before 2017-12-31, whichever comes first
When submitting NDA, ICH Common Technical Document (CTD) Format should be used.
## Technical Document

<table>
<thead>
<tr>
<th>Quality</th>
<th>Non-Clinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source Controls</td>
<td>• Pharmacology (relevant animal models of disease; injury if possible)</td>
<td>• Current clinical experience</td>
</tr>
<tr>
<td>(Reagents, Excipients)</td>
<td>• Toxicology (relevant healthy animal species)</td>
<td>• Study design (administration procedure, proposed dose levels, regimen, escalating)</td>
</tr>
<tr>
<td>Virus or Cell Banks</td>
<td></td>
<td>• Selection of patients (inclusion/exclusion criteria)</td>
</tr>
<tr>
<td>(Size, Passage number)</td>
<td></td>
<td>• Safety evaluations</td>
</tr>
<tr>
<td>Characterization</td>
<td></td>
<td>• Efficacy evaluations</td>
</tr>
<tr>
<td>Manufacturing</td>
<td></td>
<td>• Statistical considerations</td>
</tr>
<tr>
<td>Process Control</td>
<td></td>
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<tr>
<td>Safety issues</td>
<td></td>
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<tr>
<td>• Sterility</td>
<td></td>
<td></td>
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<tr>
<td>• Purity/Impurities</td>
<td></td>
<td></td>
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<tr>
<td>• Identity</td>
<td></td>
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<tr>
<td>Efficacy issues</td>
<td></td>
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<tr>
<td>• Potency</td>
<td></td>
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<tr>
<td>• Stability</td>
<td></td>
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<tr>
<td>Batch analysis</td>
<td></td>
<td></td>
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<tr>
<td>Stability</td>
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</tbody>
</table>
Expedited Programs for NDA

NDA review track

- Regular
  - Standard Review (360 days)
  - Abbreviated Review (180 days)

- Unmet medical need
  - AA applicable

- Priority Review (240 days)
- Priority + Abbreviated

*Abbreviated Review: NCE + US FDA, EMA, MHLW approved (2 in 3)
*AA: Accelerated approval (AA): Surrogate endpoint CT accepted
Streamline Review Procedure

- Establishing “Review process and Timeline” (2016)
- Amending “Review time for non-NCE NDA” (2016)
- Announcing “Refuse-to-File” (2016)
- Trying-out “Pre-NDA meeting” (2016)
- Announcing “Points to consider for all types of NDAs” (2017)
- Establishing “On-line submission platform”

Consultation and Rolling Review (2016)

Quality、Efficiency、Consistency、Transparency、Clarity、Predictability
Outline

1. Organization and Responsibility of TFDA
2. Current Regulatory Framework
3. Application and Evaluation Process
4. Points to Consider on Vaccine (Case Study)
5. Future Prospects
Application Process

<IND> Applicants (Sponsor, CRO, Hospital)

Consultation

Registry on Taiwan Clinical Trials Network

Submission
Administrative part and Technical part

User Fee
30,000 NTD

<NDA> Applicants (Sponsor)

Consultation

Submission
Administrative part and Technical part

User Fee
800,000 NTD

Registration
Evaluation Process

Application submitted to TFDA

Documentation Evaluation

Integrated Medicinal Products Review Office (iMPRO)

<table>
<thead>
<tr>
<th>Administrative part</th>
<th>Technical part</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC</td>
<td>Pharm/Tox</td>
</tr>
<tr>
<td>PK/PD</td>
<td>Clinical</td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
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</tbody>
</table>

Assessment Report

Advisory Committee

Asking for suggestion
When necessary
Providing opinion

Final Decision made by TFDA

IND: 30 days
NDA: 360 days
Consultation System

- Online Information
- Consultation by Request
- Active Consultation
- Industrial Communication Platform

Domestic Innovative Consultation (Early Harvest Lists)

National Research Program for Biopharmaceuticals (NRPB)
Domestic Innovative Consultation

To facilitate medicinal products development and marketing approval

What is needed at consultation?
- Well-developed & controlled manufacturing information
- Preclinical studies to show safety and effect of products
- Provide evidence to support human dosing and scientific rationale

Meeting types:
- Kick-off meeting
- Sponsor meeting
- Pre-filing meeting

Rolling Review

Regular path
- Pre-Clinical
- Phase I
- Phase II
- Phase III
- NDA Review

Consultation
- KO
- P
- S
- P
- S
- P
- S
- P

Domestic Innovative Consultation

Meeting types:
- Kick-off meeting
- Sponsor meeting
- Pre-filing meeting

Rolling Review

Regular path
- Pre-Clinical
- Phase I
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Consultation
- KO
- P
- S
- P
- S
- P
- S
- P
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Points to Consider on Vaccine

Products containing antigen that are intended for use in the prevention, mitigation, treatment, or cure of a disease or infection by stimulating an immune response.

- The marketing application contains all of the data gathered during preclinical studies and human clinical trials. Sponsors should demonstrate **Safe, Pure and Potent**. Regulators review all of these data to determine whether the data support licensure for marketing authorization.
- For a successful product development, manufacturing control and **keep product consistency** are very important factors.
- Science provides the information, but science does not provide all of the answers. Regulators to make decisions **based on the benefits and risks for the public health**.
Incremental Requirement Development

Specifications for Lot Release Testing
- Phase 1-2
  - Safety, acceptance limits may have wider ranges
- Phase 3- pivotal studies
  - tests more refined and acceptance criteria more defined; established limits for release assays
- Product registration
  - specifications based on validated assays
Outline

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Vaccines have unique considerations for product and clinical development. (highly regulated biologics, high risks of starting materials, fully aseptic process, for healthy individual use, children or elders)

Regulation and guidance facilitate the development of quality, safety, and efficacy new vaccine products.

Vaccines manufactured consistently according to PIC/S GMP, and Post-marketing safety evaluation system is important.

Exploring novel technologies for new vaccines may provide important alternatives to address infectious diseases. (cell-based and recombinant manufacturing technology, novel adjuvants, or delivery system)

Regulatory staffs continue to support the science-based review and regulation of vaccines and related products.
Regulatory Cooperation

To Regularly participate in international activities to acquire update information

To develop the training program with regulators to stimulate scientific principles to enhance Quality, Safety and Efficacy of medicinal products

• Collaboration with Taiwan CDC on the vaccine safety data, vaccine adverse event reporting system
• Intense oversight of the production of vaccines continues after licensure to ensure continuing safety

To establish personal exchanges mechanism with regulatory agencies to identify possible topics for harmonization or regulatory convergence from basic to clinical

Step in to Taiwan Today
Step out to the World Tomorrow
Triple-Win Situation

Consumer Protection

Win-Win-Win

Government
Smart Administration

Industry
Competences Enhancement
Thank You for Your Attention