청렴韓세상

국민의 더 건강한 내일을 위한 정부혁신
보다 나은 식약처

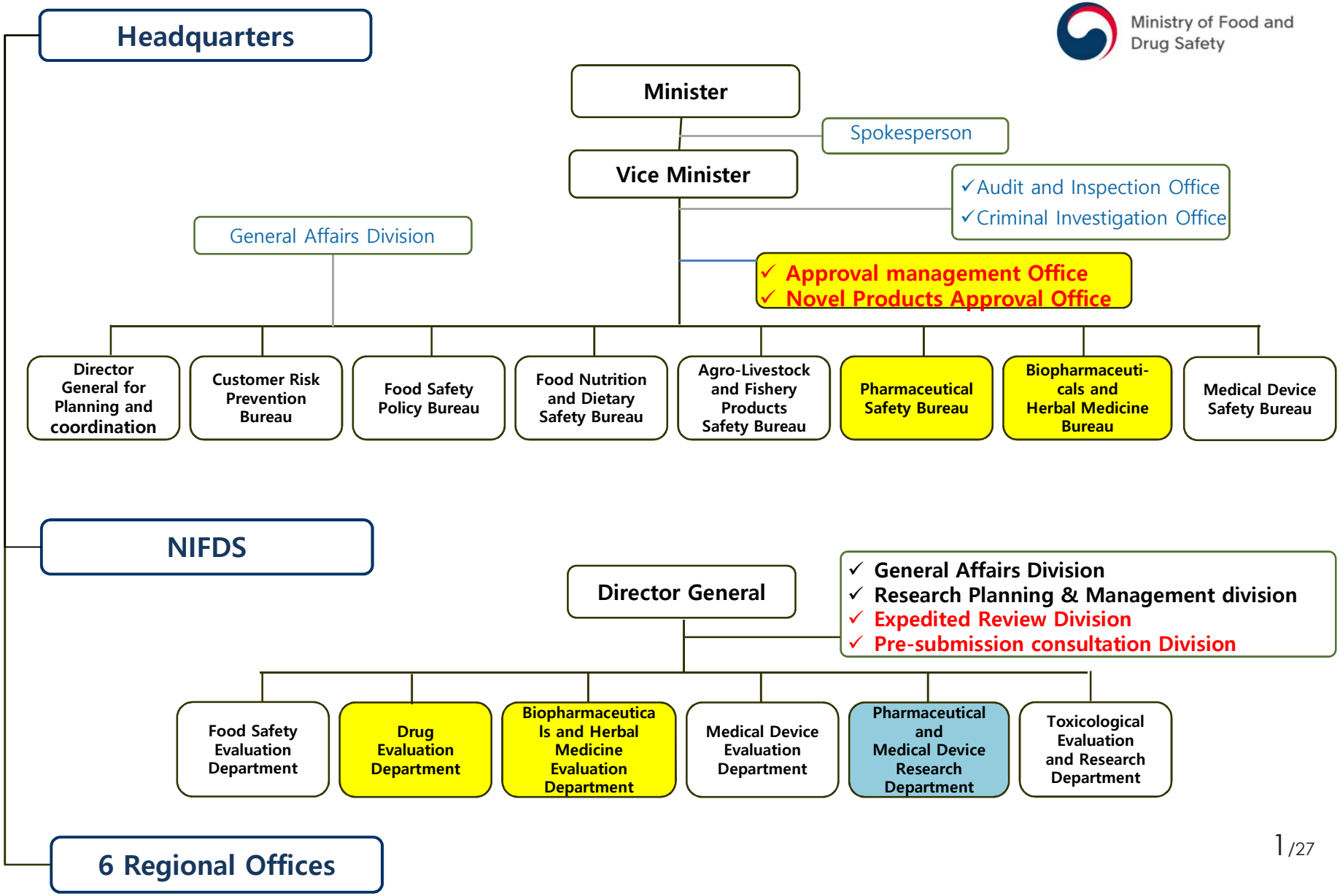
Recent Trends in Drug Quality Reviews

Mijeong Kim, Ph.D
Pharmaceutical Standardization Division
Drug Evaluation Department
NIFDS, MFDS Korea

Ministry of Food and Drug Safety

National Institute of Food and Drug Safety Evaluation

MFDS Organization



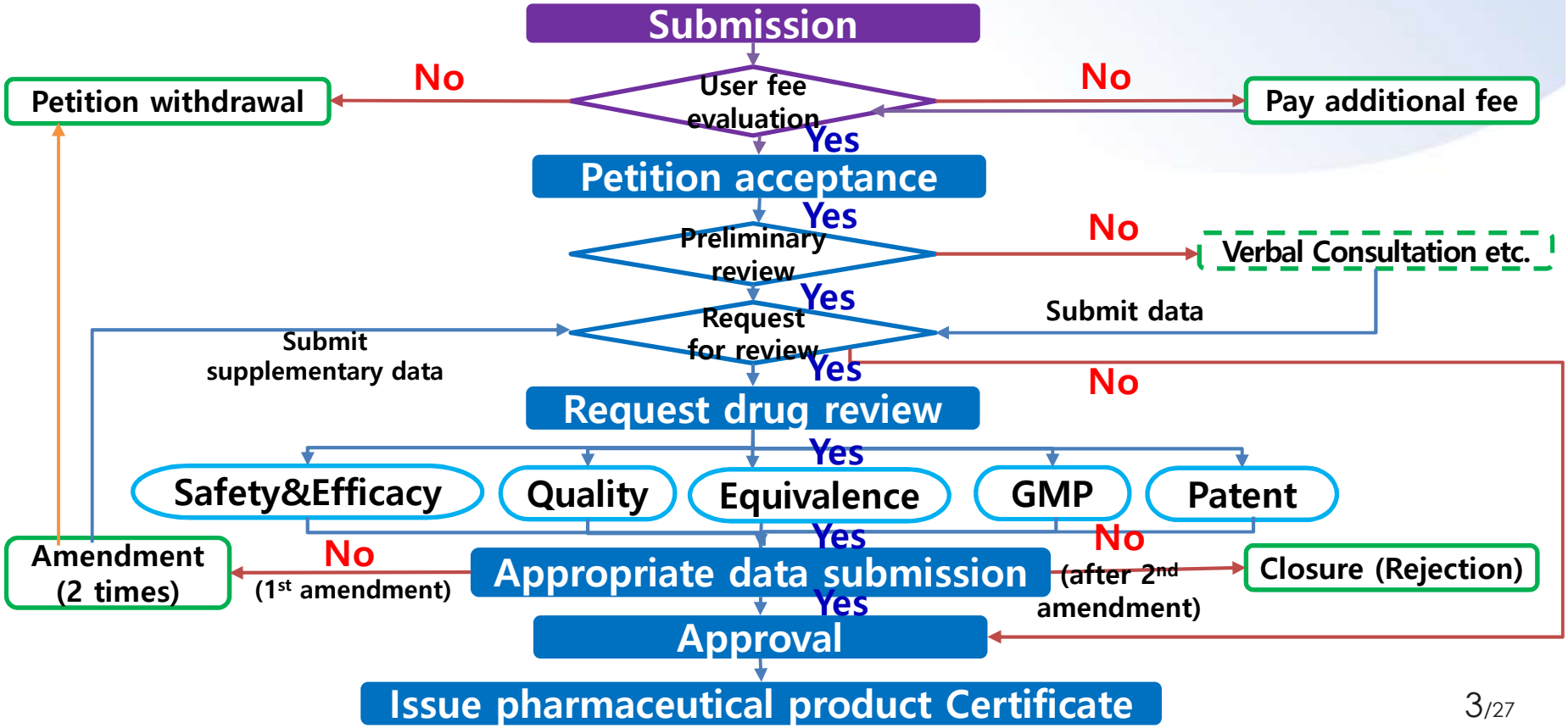
Ministry of Food and Drug Safety

Drug Approval System in Korea

Drug Approval Process in Korea

Approval of drug products

- **(Overview)** Approve drug products (incl. drug substances) qualified by technical review and inspection for safety, efficacy and quality



Ministry of Food and Drug Safety

Classification of Products

Pharmaceutical (Chemical Entity)

- Products, other than quasi-drugs, among the articles listed in the Korean Pharmacopoeia
- Products used for the purpose of diagnosis, medical care, alleviation, treatment or prevention of diseases of human beings or animals, excluding appliances, machinery or equipment
- Materials, other than appliances, machinery or equipment, used for the purpose of exerting pharmacological effect upon the structure or functions of human beings or animals

Biological Product

- A medical product that is manufactured with raw materials or substances derived from human or other organisms
- Biologics, recombinant DNA product, cell culture-derived product, cell therapy product, gene therapy product

Herbal Medicine

- Korean traditional drug preparation: a drug made or mixed with Korean traditional medicine following the principle of Korean traditional medicine
- Herbal Medicine: Natural preparations recognized in western medicine and aren't used for the purpose of Korean traditional treatment

Ministry of Food and Drug Safety

Drugs for approval & notification

Drugs for approval

- New Drugs
- Drugs requiring safety and efficacy review other than new drugs

Drugs subject to data submission

IMD*

Generic Drugs
(Subject to BE study)
- New drugs since Jan. 1, 1989
- Substances subject to BE test
- Special dosage forms (e.g. extended release)

Others (e.g. new excipients, revision of approvals)

Drugs for notification

- Product items listed in KP or Pharmaceutical Codex approved by the Minister
- Product items listed in Korean Herbal Medicine Pharmacopoeia
- Product items that meet Standard Manufacturing Monograph
- Product items for which the specification and test method were separately announced by the Minister
- Product items which are identical to approved product items

*Incrementally Modified Drug

New drug, drug for data submission & IMD

New Drug

Drugs of new materials, the chemical structure or the composition of substance of which is new, or a drug of combination preparation containing new materials

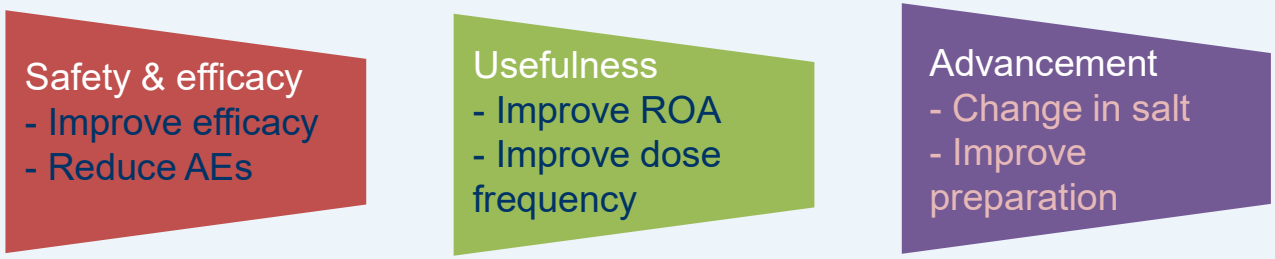
Drug subject to data submission

Drugs except new drugs requiring safety and efficacy evaluation

- New salt and isomer
- Group of new efficacy
- Increase/decrease in new composition or content
- New route of administration
- New dosage

Incrementally Modified Drug

- a pharmaceutical requiring data submission that the Minister acknowledged
  - improvement in **safety, efficacy, usefulness** (administration compliance, convenience etc.) compared with an previously approved pharmaceutical
  - **advancement** in medicinal and pharmaceutical technology

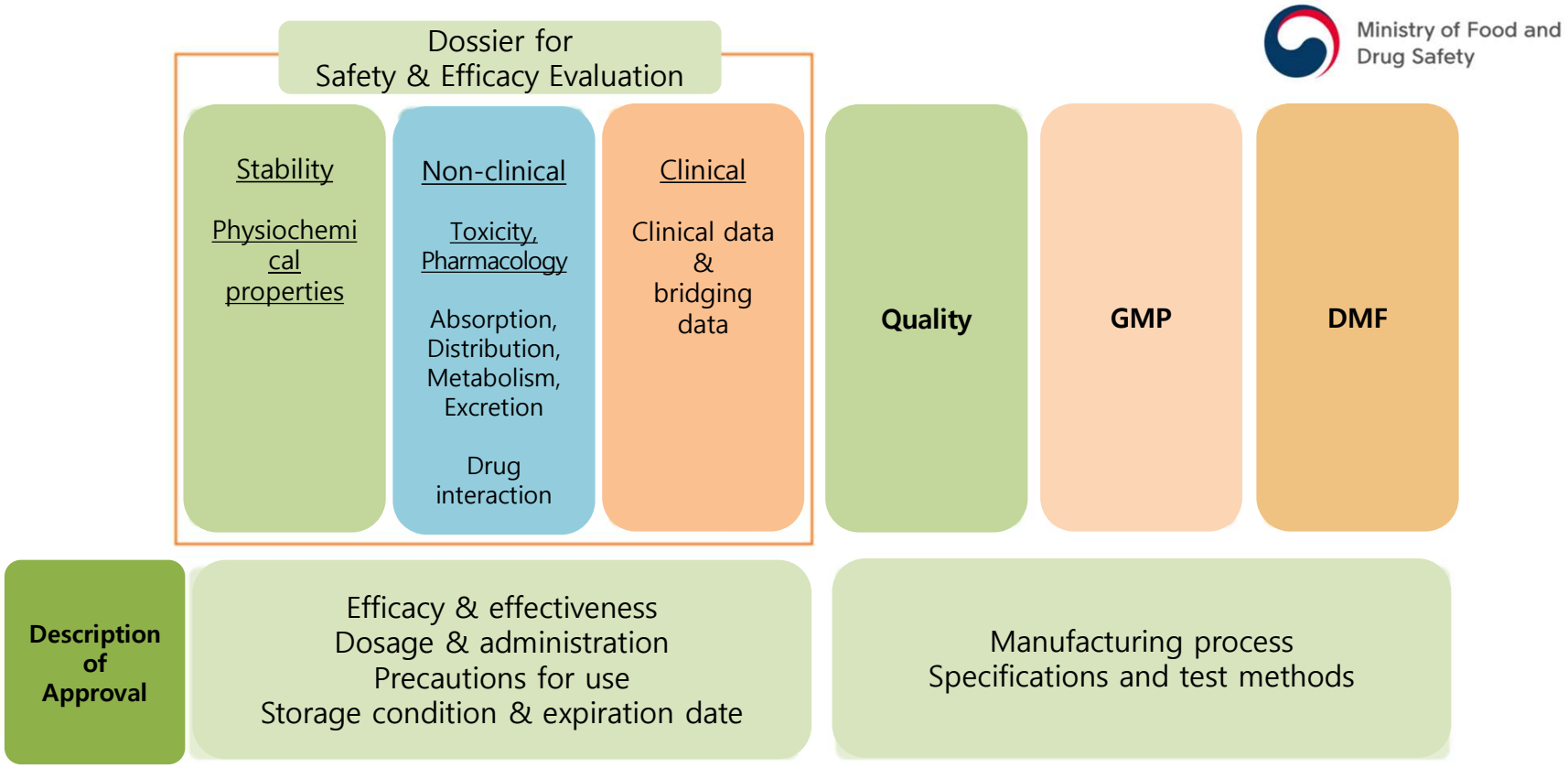


Data requirement for approval

Required application dossier for approval

- **(New Drug)**

① Safety and efficacy data
② Specifications and test methods
③ Data on bioequivalence test or comparative clinical trial
④ Certificate of manufacturing and marketing (for imported products)
⑤ Data on comparative dissolution
⑥ Evaluation data of GMP inspection
⑦ Drug Master Files (DMF)
⑧ Manufacturer of API
⑨ Agreement for contract manufacturing
⑩ Patent certification
⑪ Data on Risk Management Plan (RMP)



- **(Drugs subject to data submission)**
  - Certain dossiers among data required for new drugs to evaluate safety and efficacy
    * Quality data are the same. DMF are required for some materials
- **(Generic Drugs)**
  - Data on bioequivalence test and quality
    * Quality data are the same. DMF are required for some materials

Ministry of Food and Drug Safety

Data required for quality review

Data for Drug Substance	Data for Drug Product
1. Structure elucidation 2. Physiochemical properties 3. Manufacturing process 4. Specifications and test methods 5. Supporting data for specifications and test methods 6. Test results 7. Reference standard, reagents and test solutions 8. Container and packaging	1. Drug ingredients and quantities 2. Manufacturing process 3. Specifications and test methods 4. Supporting data for specifications and test methods 5. Test results 6. Reference and standard, reagents and test solutions 7. Container and packaging
* Safety data	* Safety data

Ministry of Food and Drug Safety

Recent trends in Drug Quality Review

Change in regulatory environment

- Pursue international harmonization in safety management system of pharmaceuticals by joining ICH, PIC/S etc.
- Pharmaceutical safety issues such as detection of NDMA impurities unintentionally included in drug products for high blood pressure and diabetes

➡ Need to strengthen quality evaluation system, especially for control of impurities

➡ Need to improve post approval change management to secure the life-cycle quality of drugs

- Accelerate the development of advanced technology applied products

➡ Need to develop standards for approval & review of products applied with advanced technologies

Milestones for improving quality review in Korea

Ministry of Food and Drug Safety

- Require more quality data for generics
  - Submit data on development, manufacturing methods, stability, container and packaging along with specifications & test methods
- Mandatory to submit CTD data for generics & drugs requiring data submission

- Stepwise expansion of DMF registration (2017)
- Require to verify the drug safety of genotoxic impurities (2019)
- Introduce individual standards for elemental impurities (2019)
- Introduce pre-registration system of drug substance (2020)

- Introduce a management system of CTD-based approval and 3 levels post-approval change
- Conduct quality evaluation for changes in manufacturer, manufacturing process, change in container
- Establish regulations for products applied with design space and RTRT

Ministry of Food and Drug Safety

TABLE OF CONTENTS

1 International harmonization in quality review

2 Life-cycle quality management

3 Strengthen impurity control

4 Establish regulations on products with advanced technology

5 Revision of related regulations

1 International Harmonization in quality review

Expand products subject to BE test

Expand to include all prescription drugs

Current regulation	Revision
● Among prescription drugs, substances announced by MFDS, some dosage forms (tablets, capsules, suppositories etc.)	● All prescription drugs **(implementation by October 2023)**

» It is mandatory to **conduct BE or comparative dissolution test** of all prescription drugs for drug approval application and post approval change in API manufacturer and manufacturing process of drug product

International harmonization in managing manufacturing methods

Ministry of Food and Drug Safety

CTD-based management of manufacturing methods

Current regulation

- CTD is required for new drugs, drugs requiring data submission & generics subject to BE test among prescription drugs
- Management with simple description of manufacturer of APIs, major process andz manufacturing site under the approval system

Revision

- Mandatory to submit CTD for all prescription drugs
- Review the whole dossier of CTD module 3 under the approval system

» For prescription drugs, **make CTD submission mandatory and manage the data of CTD module 3** (drug substance and product) **under the approval system**

Strengthen quality review on compendium-listed products

Ministry of Food and Drug Safety

Require quality data for compendium-listed products

Current regulation	Revision
● Waiver of specification and test methods for products listed in compendium	● Need to submit quality data for prescription drugs listed in **compendium** **(implementation in October 2021)**

» For prescription drugs, **it is necessary to submit quality data** even though the product is listed in compendium.

* **'Guideline of test method verification'** is planned to develop to verify the test methods in compendium

2 Life-cycle quality management

Improve the system of post approval change

Ministry of Food and Drug Safety

Graded management of post approval change by risk-based approach

Current regulation

- Pre-application for post approval change in pharmaceutical product license

Revision

- The total CTD Module 3 shall be subject to approval review
- Graded management with pre-application for **post approval change, pre-marketing reporting and annual reporting**

» Introduce the **management system of 3 levels post approval change considering the impact of the change on quality and efficacy of drugs**

* A guideline is under development describing requirements of data submission for change in sections of CTD

Improve the system of post approval change

Ministry of Food and Drug Safety

Strengthen quality review of post approval changes (manufacturing processes, container etc.)

Current regulation

- Data on BE test should be submitted when manufacturing process are changed
- No need for drug review when it comes to change of immediate container

Revision

- Submit both **data on equivalence test(BE or comparative dissolution) and quality evaluation** for change in manufacturing process
- Submit **data on stability test** for change of immediate container **(implementation in May 2021)**

» **Changes of API manufacturer, manufacturing process, and immediate container are subject to quality review**

3 Strengthen impurity control

Require the submission of impurity evaluation data

Ministry of Food and Drug Safety

Require safety data of genotoxic impurities

Current regulation

- Submission of data on impurities

Revision

- Data on impurities
- Data on **genotoxic** and **carcinogenic** impurities
- Data on **elemental impurities** **(implementation in September 2020)**

» It is mandatory to **verify the safety** of drugs against possible introduction of **genotoxic impurities and elemental impurities**

Strengthen management of drug substance quality

Ministry of Food and Drug Safety

DMF system improvement

Process

	Application	→	Quality review	→	Registration	
Process Improvement (June 2020)	Application	→	Check quality data submission	→	Prior registration (Filing)	→ Quality review along drug products → Registration

✓ Apply for drug product approval or prior-review

Target

- **Mandatory to register** unregistered **APIs of approved drug products**

*** Expand the scope gradually to complete all registration by June 30, 2023**

4 Establish regulations on products with advanced technology

Establish regulations for review of advanced technology applied products

Ministry of Food and Drug Safety

New regulations for quality review of QbD applied products

QbD products

- Allow **annual reporting for changes within design space** with no prior authorization

Release testing exemption

- **Permit Real time release testing and provide how to fill out the related form with examples**
- **Allow to manage periodic or skip testing**

5 Revision of related regulations

Status of related regulations for quality review

Ministry of Food and Drug Safety

Mandatory for all prescription drugs to submit equivalence data

- Regulation on the safety of medical products etc. (revised in October 2020)
- Regulation on management for pharmaceutical equivalence test (Administrative Notice within 2020)

CTD-based approval management & 3-phase approval change

- Regulation on Pharmaceuticals Approval, Notification, and Review (Administrative Notice within 2020)

Quality evaluation for changes in manufacturing methods, manufacturers

- Regulation on Pharmaceuticals Approval, Notification, and Review (Administrative Notice within 2020)

New regulations for quality review of products applied with design space, RTRT

- Regulation on Pharmaceuticals Approval, Notification, and Review (Administrative Notice within 2020)

Thank You !

Ministry of Food and Drug Safety

National Institute of Food and Drug Safety Evaluation