Korea GMP & DMF

April. 2015

Korea Pharmaceutical Traders Association
Deputy director
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Contents

KPTA

KOREA PHARM

Korea Pharmaceutical Traders Association

KPTA

☐ **Purpose**

- ㅇ Trade promotion of pharmaceuticals, cosmetics, etc
- ㅇ Quality control and assurance of imported pharmaceuticals, etc

* Based on Article 67 of the pharmaceutical affairs law, Article 15 of the cosmetics act and the Article 32 of the civil law

☐ **Scope of business**

- ㅇ Promotion of exports via overseas market development, exhibitions and market survey
  - Sending market development team (2 times a year)
  - Set up Korea Pavilion in China, Japan, Europe and Indonesia
  - Holding CPhI Korea in Korea since 2014

KPTA

- Submitting petition on pharmaceutical affairs to the government
- Issue pre customes declaration for imported medical drugs, in vitro diagnostics, API, cosmetics, etc. to the customs by EDI (Electronic Data Interchange)
- Collect import/export statistics
- Review parallel imported cosmetics
- Quality control for the imported products by Korea Pharmaceutical Test & Research Institute
  * Medical drugs, cells, vaccines in vitro diagnostics, herbal medicine, cosmetics
  * Bioequivalence test, clinical phase 1 test
  * Quasi drugs

Pharmaceutical industry

Pharmaceutical industry

(Unit : trillion won, %)

Classification	2011	2012	2013
Production	15.5	15.7	16.3
Export	1.9	2.3	2.3
Import	5.5	5.8	5.2
Trade balance	-3.5	-3.5	-2.9
Market scale	19.1	19.2	19.3
Share of Import	28.8	30.4	27.3

- Market scale: (production+import)-export

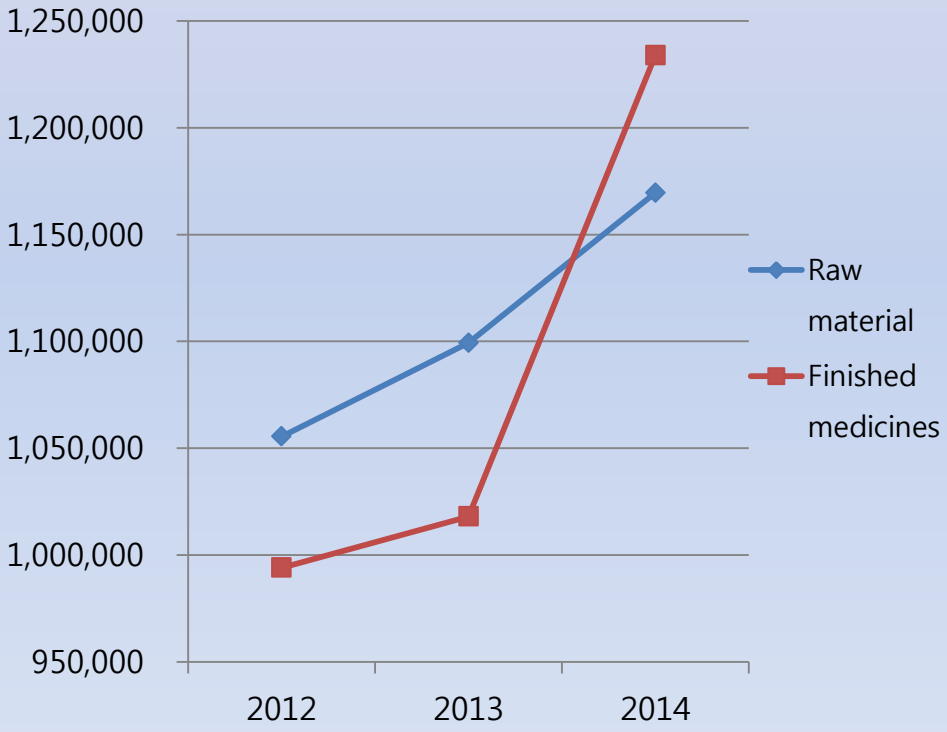
Pharmaceutical industry

■ Export (‘12 ~’14)

(Unit : US$ 1,000)

	2012	2013	2014
Raw material	1,055,463	1,099,284	1,169,558
Finished medicines	994,030	1,018,010	1,233,932
Total	**2,049,493**	**2,117,294**	**2,403,490**

(Unit : US$ 1,000)



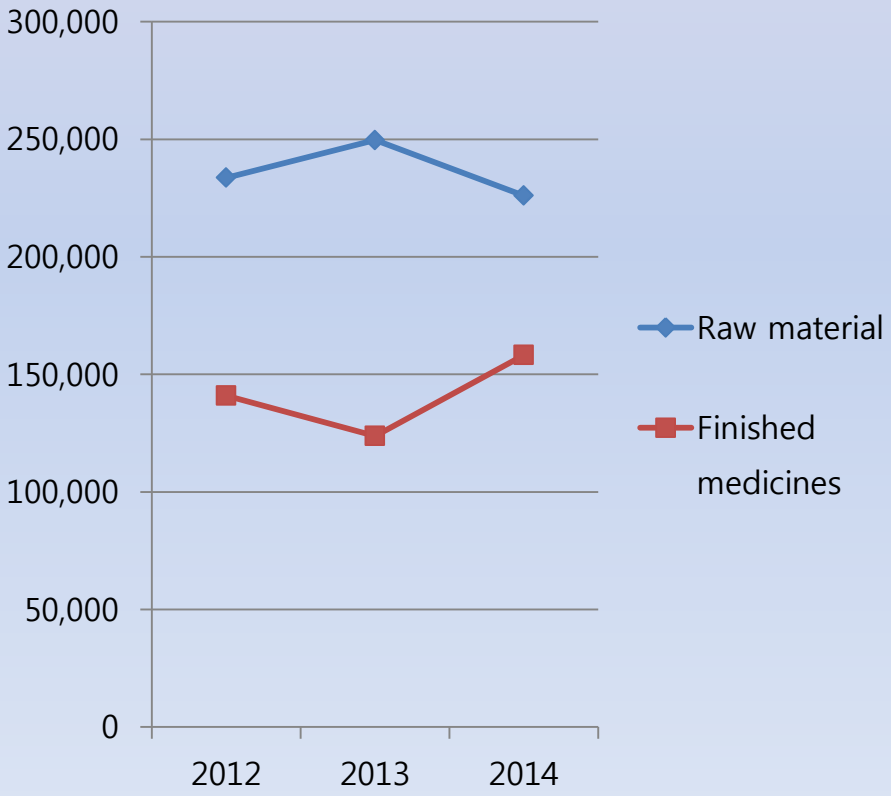
Pharmaceutical industry

■ Export to Japan (‘12 ~’14)

(Unit : US$ 1,000)

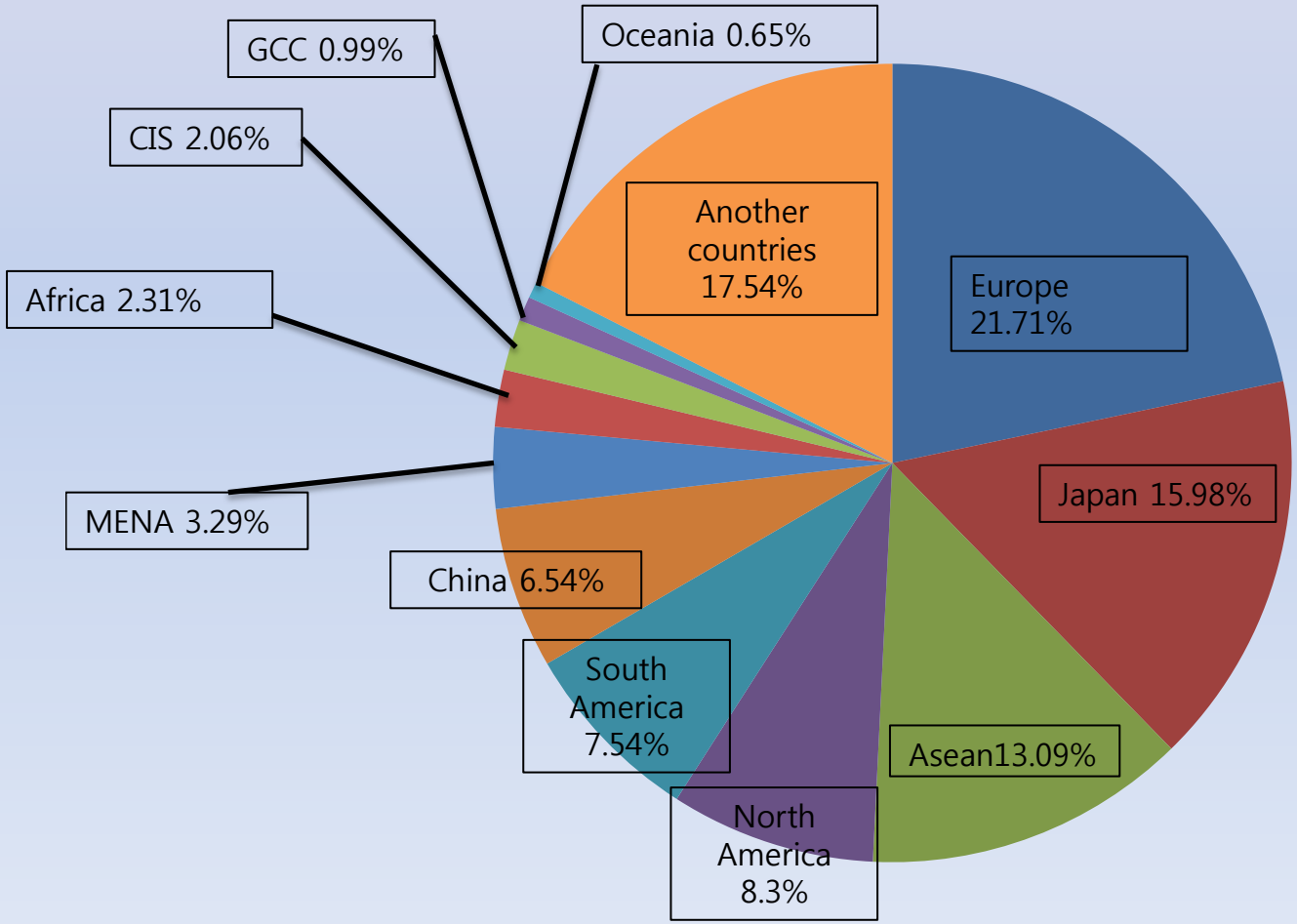
	2012	2013	2014
Raw material	233,637	249,615	225,990
Finished medicines	140,935	123,793	158,215
Total	**374,572**	**373,408**	**384,205**

(Unit : US$ 1,000)



Pharmaceutical industry

Export Status on every blocks



KGMP

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KGMP

- Good Manufacturing Practice

- GMP requirement is different according to each countries but the purpose is same

  - USA : 1962
  - Japan : 1974
  - Korea : 1977

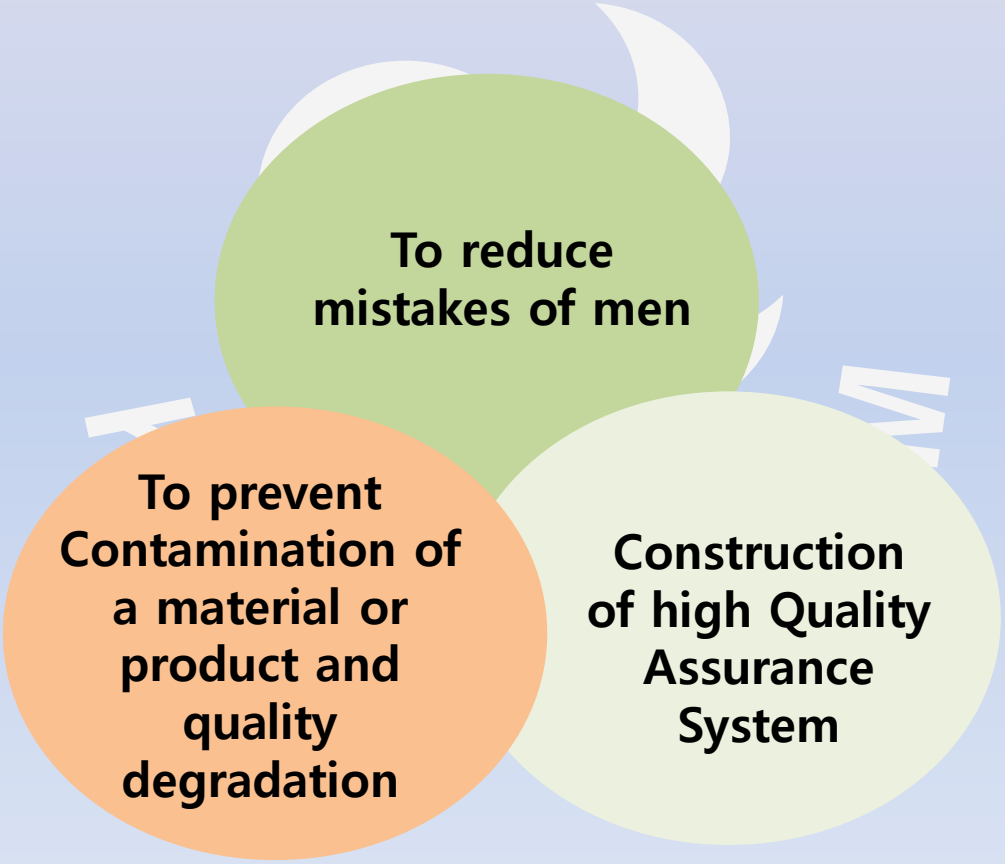
KGMP

■ Background of the Establishment of KGMP

Year	Description
1969	Advisory from WHO on GMP implementation
1974	Launch of the KGMP Research Committee
1977	Promulgation of the KGMP standards (Ministry of Health and Social Welfare Regulation No. 373)
1978	Announcement of the KGMP Enforcement Guideline and recommendation of autonomous implementation for manufacturers
1994	Compulsory implementation of KGMP
2014. 07. 01.	Joining PIC/S

KGMP

■ The Goal of KGMP



KGMP

< Comparison with international GMP and new KGMP >

Criteria	WHO	PIC/S	EU	Japan	Singapore	Korea
Pre-approval GMP Evaluation	○	○	○	○	○	○
Validation	○	○	○	○	○	○
Management of Automatic system equipment	○	○	○	○	○	○
Deviation Investigation	○	○	○	○	○	○
Qualification	○	○	○	○	○	○
Change control	○	○	○	○	○	○
Self-Inspection	○	○	○	○	○	○
Annual Quality Assessment	○	○	○	○	○	○
Stability Test	○	○	○	○	○	○
Management of Clean Area	○	○	○	○	○	○

KGMP

■ Required Documents for GMP Evaluation

1. Floor plan of the manufacturing plant (electronic file attachment)
2. Documents on the work areas connected with the item under review (electronic file attachment)
   a. Floor plan of the work areas labeled with the cleanliness grades, differential pressure between work areas, and flow of human traffic and material transport
   b. List of machines and equipment used in manufacturing and testing and arrangement diagram of the machinery
   c. Schematic diagrams of the air conditioning facilities and the compressed air and service water treatment systems
3. Documents on the facilities connected with the item under review and environmental management
   a. Management of water used in manufacturing
   b. Management of automated devices, etc.
   c. Management of cleanliness
4. Documents on the GMP organization chart and quality management (assurance) system
5. Document management policy and list of documents
6. Copies of the product standards and manufacturing and quality management records in relation to the item under review
7. Validation data in relation to the item under review

※ Documents need not be submitted if they were already submitted for approval (must provide the name of the approved product)

※ Documents in foreign languages must be translated into Korean before their submission

KGMP

■ Amendments to the Regulations on Manufacturing & Quality Management (GMP)

○ Amendments to the Regulations on Safety of Pharmaceuticals, etc. (Aug. 21, 2014)

- **Expanded scope of application of GMP evaluation for pharmaceutical approval**
  - Required documents for GMP evaluation need to be submitted by applicants requesting approval of orphan drugs, pharmaceuticals for which there are standard manufacturing specifications, radiopharmaceuticals, and medical high-pressure gases

- **Improved GMP standards**
  - Compulsory performance of validation and post-market stability testing of non-sterile herbal medicine preparations

- **Newly established GMP standards for raw materials, radiopharmaceuticals, medical high-pressure gases and pharmaceuticals under clinical trials**
  - Separate GMP standards from the GMP standards for drug products
  - The prescribed GMP standards must be observed for 2 years after the enforcement date in the case of radiopharmaceuticals, and medical high-pressure gases

KGMP

■ Amendments to the Regulations on Manufacturing & Quality Management (GMP)

○ Amendments to the Regulations on Safety of Pharmaceuticals, etc. (Oct. 10, 2014)

- **Issuance of a certificate of conformity based on the pharmaceutical manufacturing and quality management standards**

  - Performance of a GMP conformity assessment every 3 years for each manufacturing plant and issuance of a conformity report by Minister of Food and Drug Safety (Regional Administrator) 3 years within the effective period
    (Manufacturers that received a certificate of conformity pursuant to the former regulations shall be deemed to be conforming to the GMP standards according to the current regulations, provided that they must received a new certificate of conformity by December 31, 2017)

  - For manufacturers applying for pharmaceutical approval within the effective period of the certificate of conformity, the certificate may be submitted in place of the required documents for the GMP evaluation
    (excl. new drugs, biological products, injections, implants, and other pharmaceuticals announced by the Minister of MFDS)

KGMP

■ Future plans

International harmonization of KGMP's standards	
Enhancing competitiveness of the industry	■ To adopt and apply PIC/S GMP guideline ■ To introduce QbD (Quality by Design)
Advancement of KGMP's standards	

KDMF

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KDMF

■ What is a drug master file (DMF)?

- A document containing detailed information on the pharmaceutical manufacturing facilities, manufacturing method, and management system for substances fed into each process, impurities, related substances, and residual solvents, etc.

- In the case of the U.S., the raw material manufacturers may submit to the FDA a DMF on its raw materials to be used in the New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) reviews. The objective of this system is to ensure confidentiality of the information submitted by the raw material manufacturer from the manufacturers of the drug products.

KDMF

KDMF System

Under this system, applications for the registration of the pharmaceutical ingredients designated by Minister of MFDS are submitted, with detailed documents on the management thereof, and registration certificates are issued for the pharmaceutical ingredients that are deemed to meet the prescribed criteria during the review process. This information is then used in the manufacture of drug products.

KDMF

■ Background of Introducing the KDMF System

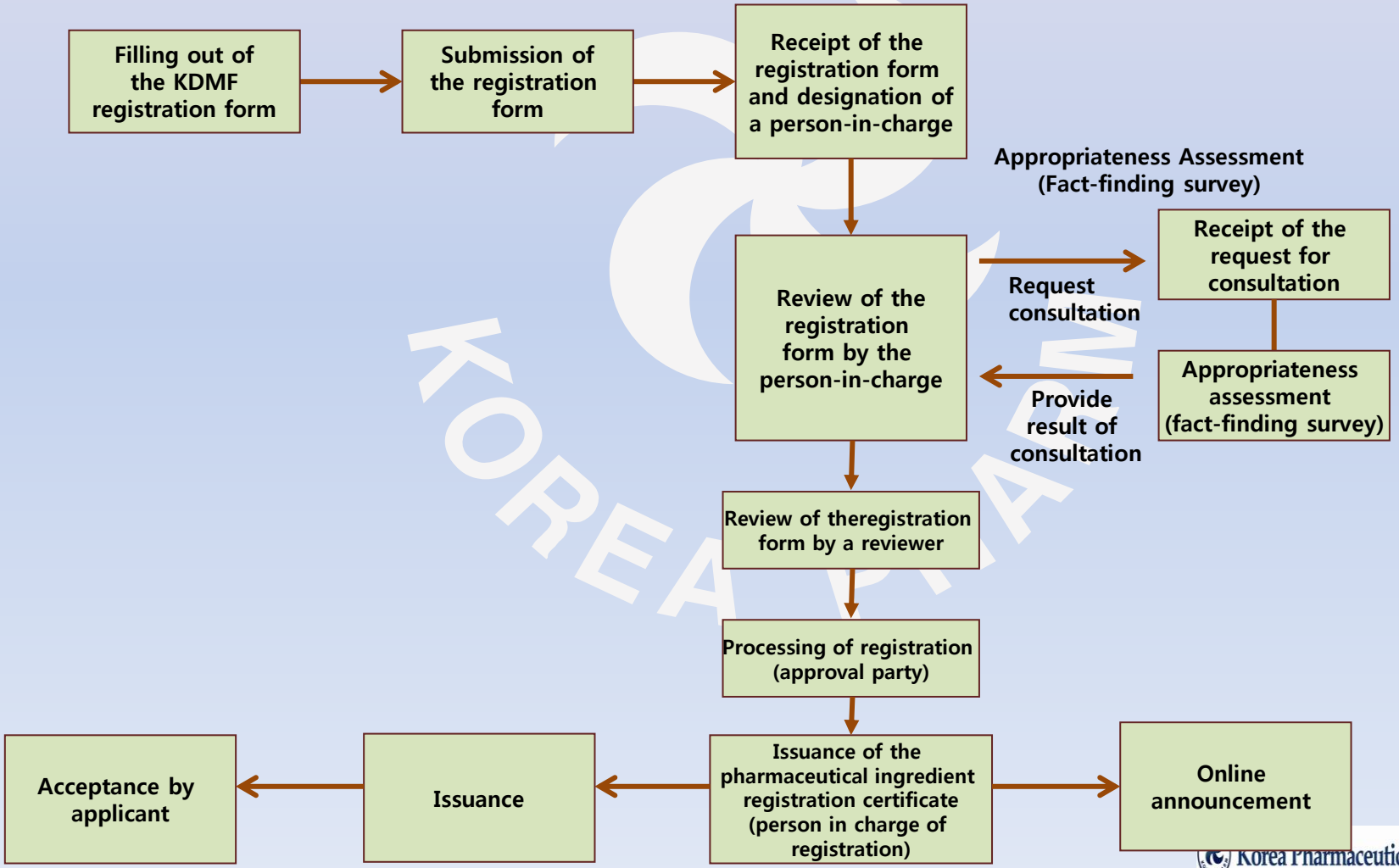
- With the compulsory implementation of GMP by drug product manufacturers (starting in May 4, 1994) followed by the compulsory implementation of GMP by pharmaceutical ingredient manufacturers(starting in July 1, 2002), there was a transition into a total GMP management system for both pharmaceutical ingredients and drug products

- A strong need for a safety management system for pharmaceutical ingredients
  - Heavy reliance on imported pharmaceutical ingredients following the financial crisis in 1997
  - 50% of the pharmaceutical ingredients were low-cost products from China and India

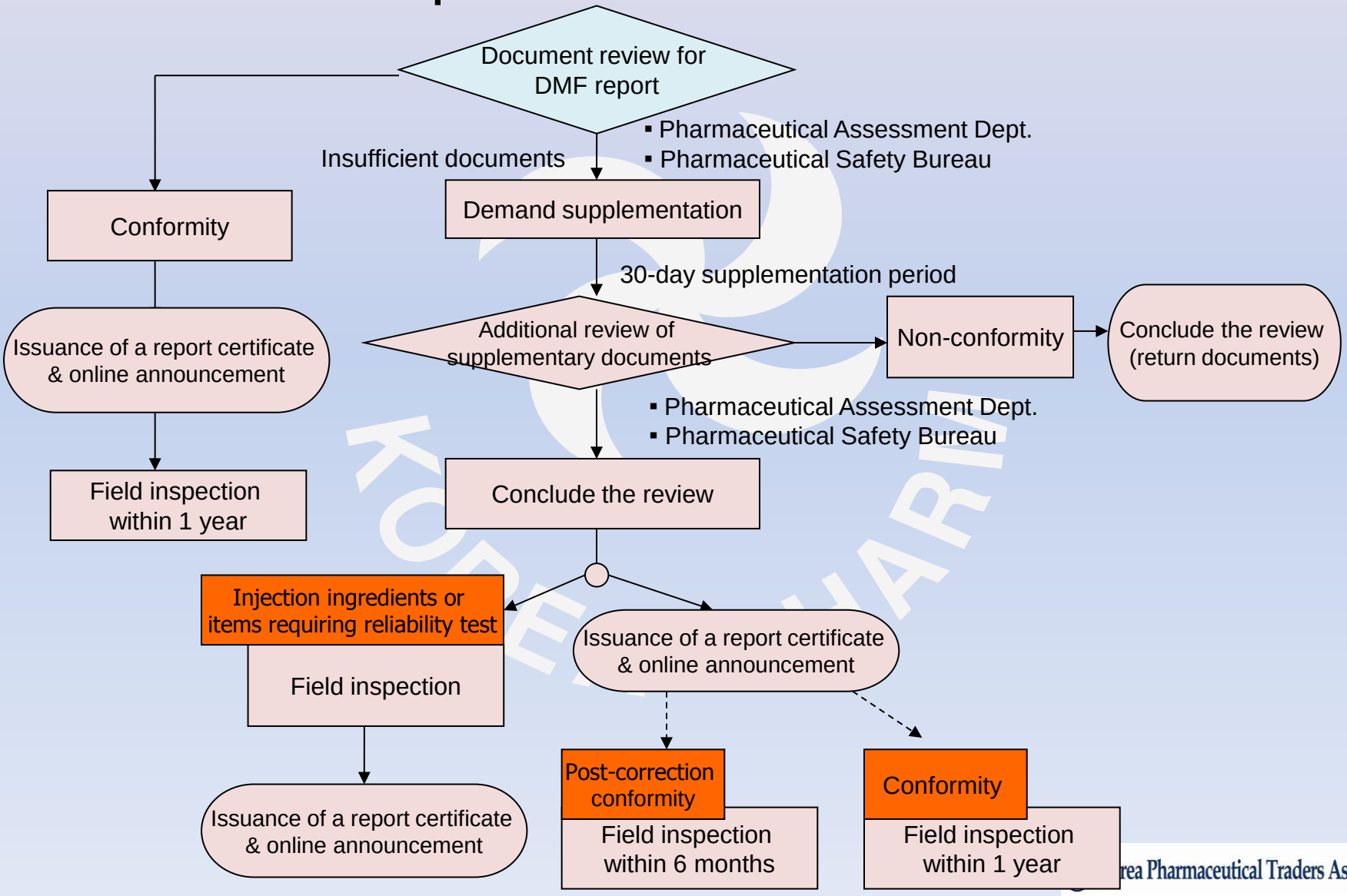
- Controversy regarding the equity between domestically produced pharmaceutical ingredients and imported pharmaceutical ingredients
  - Concerns that imported pharmaceutical ingredients are of low quality due to the lack of evaluation procedures for their production processes, etc.

KDMF

■ KDMF Registration Procedure



■ Flowchart: DMF Report Evaluation



KDMF

■ Required Documents for KDMF

- Documents on the origin and development process
- Documents on structural decisions
- Documents on the physicochemical characteristics
- Documents on stability
- Documents on the manufacturing method, packaging, container, handling precautions, etc.
- Pharmaceutical ingredient test report and documents on the analysis and solvents, etc.

KDMF

■ Registration of Changes

- Changes, if any, must be registered prior to the manufacture and sales of the pharmaceutical ingredients concerned

■ Notification of Changes

- The product concerned should be manufactured and sold, based on the changes, but the changes must be notified to the Minister of MFDS by the end of January in the following year

KDMF

■ General Items

A change of the name of the manufacturing plant, without any changes in its location, and a change of address resulting from a change in the administrative zoning must be notified

In this case, the following documents shall be submitted:

- In the case of name change, documents issued by competent authorities and notarized documents

- GMP certificate issued under the new name of the manufacturing plant or address

- A document issued by the State on the changes in the administrative zoning system (incl. electronic documents)

KDMF

■ Manufacturing Facilities

Simple changes in the layout (manufacturing and testing equipment, etc.) need not be notified

In this case, the following documents shall be submitted:

- In the case of site change (new construction, extension, relocation), evidentiary documents (Site Master File, etc.)

- In the case of site change accompanied by changes in the manufacturing method, documents on the manufacturing method and test report

Physiochemical Characteristics & Stability Test

The following documents shall be submitted:

- In the case of a name change (general name, chemical name, CAS No.), evidentiary documents such as INN list on the affected item

- In the case of obtaining additional stability test data after receiving approval for the term of use following the submission of a stability protocol, the following documents shall be submitted: stability data obtained during the term of use and stability test data on the three lots (incl. evidentiary data for 1 of the lots)

KDMF

■ **Documents on the manufacturing method, packaging, container, handling precautions, etc.**

- In the case of changing major processes or the volume of the manufacturing unit (by over 10-fold), the following documents shall be submitted: documents on the manufacturing method, documents proving the equivalence between before and after the change (impurity profiles of the former batches and new batches and statistical analysis data on the physicochemical properties such as UV and IR), and test reports (3-batch tests and evidentiary data for 1 batch)

KDMF

■ **Pharmaceutical ingredient test report and documents on the analysis and solvents, etc.**

- Changes in the testing specifications

- Changes in the testing standards:(scope of required documents prescribed in the Regulations on the Approval, Notification and Review of Pharmaceuticals is applicable mutatis mutandis)

- Changes in the test method

- Slight changes in the testing procedure for the starting materials, intermediates and reagents although the test method remains identical

Thank You.