Government Publications Registration Number
11-1471057-000122-10

www.mfds.go.kr

2015 Annual Report of National Lot Release

MINISTRY OF FOOD AND DRUG SAFETY
National Institute
of Food and Drug Safety Evalution

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Contents

1 About Us

1.1 Ministry of Food and Drug Safety

The Korea Food and Drug Safety Headquarter was established in April 1996 as an agency under the Ministry of Health and Welfare to assure the safety and health of people's lives through the supervision of food and drugs. Since then, it had enlarged and become the Korea Food and Drug Administration (KFDA), an external organization of the Ministry, on February 28, 1998. Finally, it became independent from the Ministry of Health and Welfare entirely and was raised in status to the Ministry of Food and Drug Safety (MFDS) on March 23, 2013. The MFDS supervises the overall mission to ensure the safety of all food and drugs, including livestock and fishery products, at a government-wide level.

The MDFS consists of the headquarters, the National Institute of Food and Drug Safety Evaluation (NIFDS), and six regional Food and Drug Administration (FDA). It has 1,778 employees as of Dec 2015 (582 at the headquarters, 409 at the NIFDS, and 787 at the regional FDA). The headquarters is composed of 1 office (Planning and Coordination), 7 bureaus, and 46 divisions and is dedicated to realizing the goal of having a healthy nation and promoting the well-being of society through food and drug safety.

Figure 1. The vision of MFDS

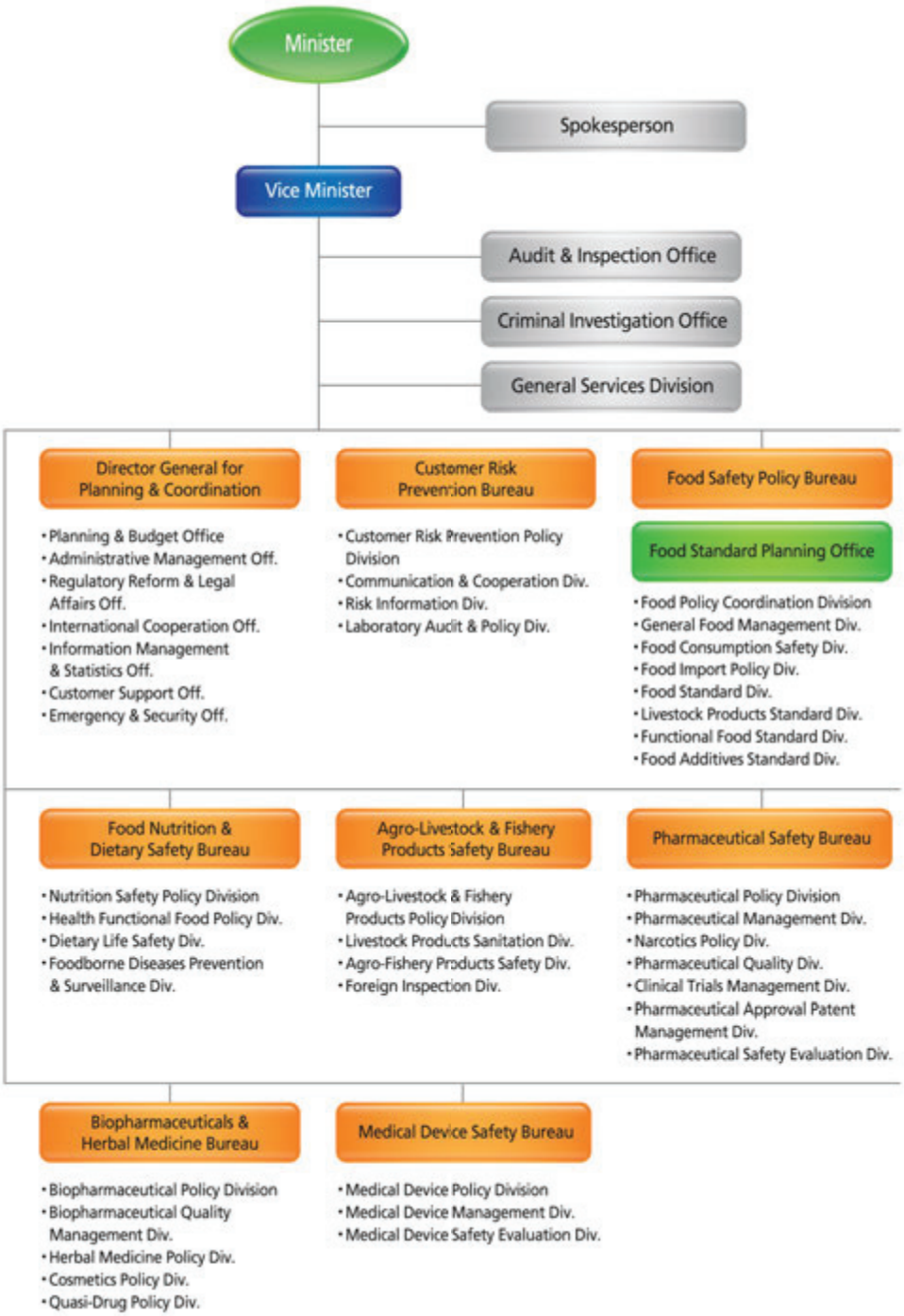

Figure 2. The MFDS headquarters's organization chart

1.2 National Institute of Food and Drug Safety Evaluation

The NIFDS was initially established as a research institute, called the National Institute of Safety Research, under the Ministry of Health and Social Affairs in December 1987. Since then, it was reorganized into the National Institute of Toxicological Research affiliated to the KFDA in February 1998 and into the NIFDS affiliated to the MFDS in March 2013.

The NIFDS currently consists of 6 departments and 40 divisions. It is dedicated to ensuring the safety of food and drugs through scientific evaluation, review, investigation, and research in order to improve the public health and the well-being of society.

Figure 3. The vision and mission of NIFDS

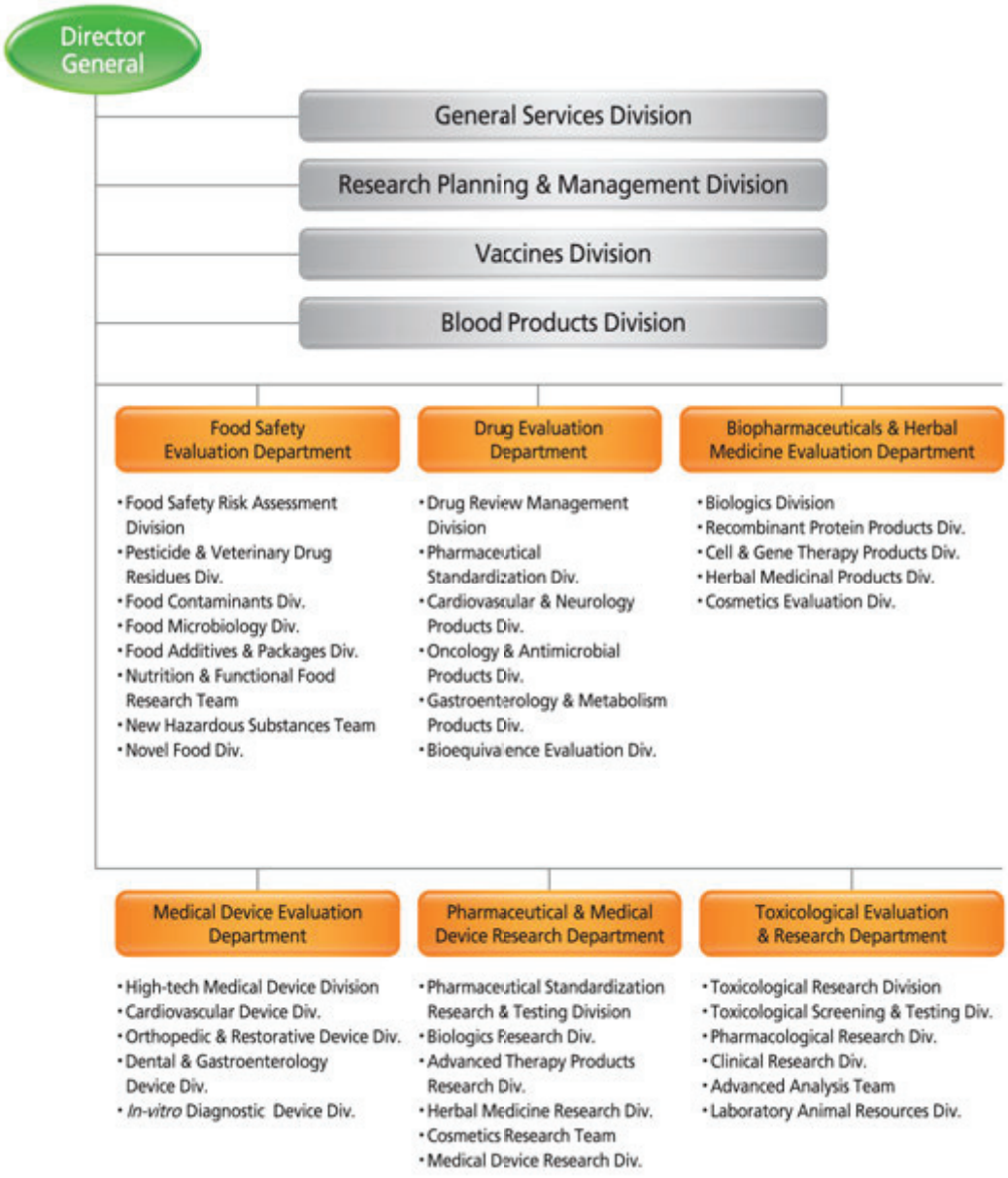

Figure 4. The NIFDS's organization chart

2 National Lot Release System

Biopharmaceuticals generally include biologics, recombinant protein products, cell therapy products, gene therapy products, *etc*.. In "Rule on the Safety of Pharmaceuticals, *etc*." and "Regulation on the Product Approval and Review of Biologics, *etc*.", biologics are defined as 'any drug product that contains organism-origin or organism-derived materials and that may include vaccines, plasma-derived products, antitoxins, *etc*., the potency and the safety level of which cannot be measured using physical or chemical tests'.

Unlike chemical drugs, biologics such as vaccines are produced using organism-origin materials, so it is difficult to maintain consistency and safety throughout the manufacturing processes. As a result, it is essential that quality control be conducted in each lot of biologics. Thus, in Korea, national lot release system has been implemented to further confirm the quality of each lot of product before it is marketed.

From June 8, 2012, in conjunction with the existing lot release testing of final drug products, our national lot release system has been put into effect to review the summary protocol for production and quality control. The summary protocol is the summarized document on manufacturing processes and test results of products, covering from raw materials to final drug products. This system has become well-established over the three years that have passed since its first implementation.

The MFDS has committed to the improvement of national quality control system for the biologics and established a comprehensive lot release system. The major improvement focuses on classification of risk of each product based on risk analysis, thus enabling the system to apply different test items for lot release in each product.

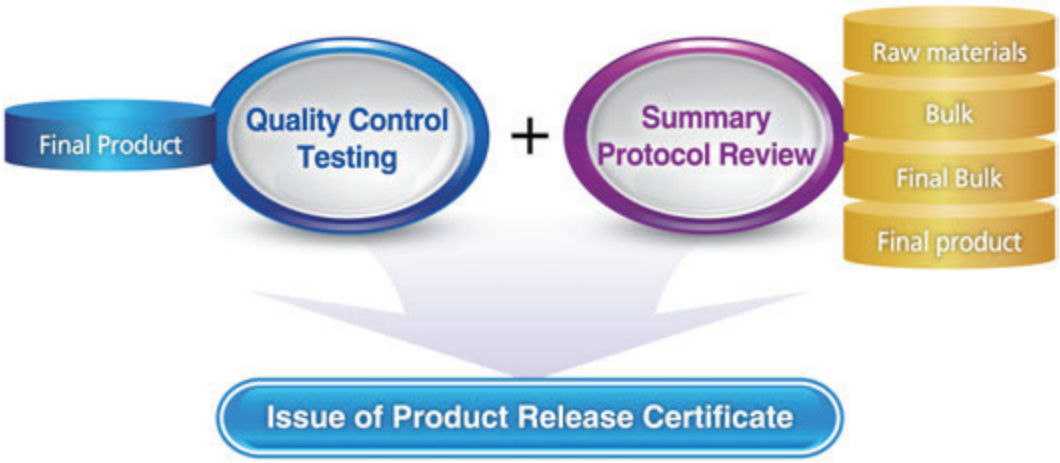

Figure 5. The national lot release system

Establishment of an effective national lot release system based on risk analysis

The existing national lot release system examines all test items for each product at first and then excludes some test items according to the performance results of the national lot release. In order to establish more advanced model of quality control, the MFDS has tried to introduce an upgraded system since 2013, so called national lot release system based on risk analysis. In relation to the improved national lot release system, “Regulation on the Designation, Approval Procedures, Methods, *etc.* of the Drugs under National Lot Release” was revised on November 27, 2014, and with a grace period of one and a half years, the revised regulation is scheduled to be enacted on April 1, 2016.

Several factors such as performance results of national lot release for each product, manufacturer's GMP observance, product approval including change approval, domestic and international informations on safety, *etc*. that are considered to affect the quality are reviewed and evaluated annually. Using these data, the level of risk is classified product by product and the tests are performed according to the test plan. In brief, when the risks are increased in products through regular evaluation in the improved national lot release system based on risk analysis, it can be applied to increase the test items of national lot release to block potential risks and strengthen the safety management practices used before the products are marketed. However, the products that consistently maintain a good quality can be exempt from lot release testing and the national lot release can be completed within 20 days by only reviewing the test report of the manufacturer/importer and the summary protocol of the product.

In October 2015, a civil affairs presentation was held on the topics of comprehensive risk assessment and notification procedures for drugs subject to national lot release. For 194 products including 38 bacterial vaccines, 102 viral vaccines, 16 botulinum preparations, 1 tuberculin, plasma derivatives, and 39 antitoxins, five categories including 1) history and results of national lot release, 2) history and results of GMP inspections for manufacturing plants, 3) domestic and foreign safety information related to the product quality, 4) items for approval of products (or revisions) that are related to the manufacture and quality, and 5) other safety information that is considered necessary to be reviewed by the Minister of Food and Drug Safety were reviewed comprehensively, and a mock evaluation was performed and the risk level was notified.

3 Related Organizations and Mission for National Lot Release

The Central Public Health Institute first started the task of implementing the national lot release in 1953, and responsibility was later transferred to the National Institute of Health, The Korea Food and Drug Safety Headquarter, and the KFDA, in that order. Currently, Vaccines Division and Blood Products Division of the NIFDS, an affiliated organization of the MFDS, are responsible for this task.

Vaccines Division has 18 employees and is responsible for bacterial vaccines, viral vaccines, and botulinum products. Blood Products Division has 8 employees and is responsible for plasma-derived products and antitoxins.

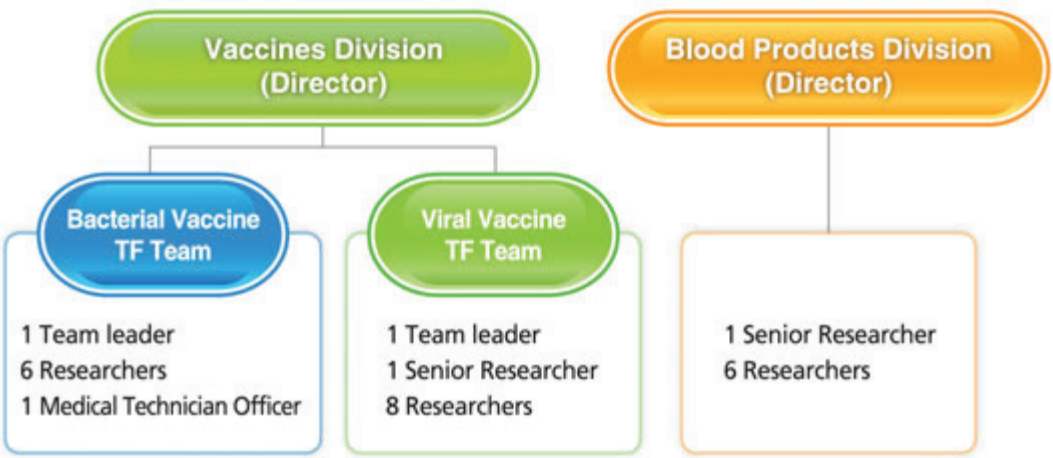

Figure 6. Organizations for national lot release

The tasks that the two divisions carry out are as follows:

❍ For bacterial vaccines, viral vaccines, botulinum products, plasma-derived products, and antitoxin

- National lot release
- Review and establishment of specification and test method
- Development of standardized test method
- Establishment of national biological reference standards
- Back-testing

❍ Maintaining and managing virus strains and cell lines

❍ Operating a World Health Organization (WHO) contracted laboratory

❍ Support for designation and investigation of quality testing organization for biologics

❍ Support for policy development and system improvement on drugs under national lot release

❍ Technical support for the safety management of human plasma for fractionation

❍ Research on related tasks mentioned above

The work flow of national lot release procedure is as follows:

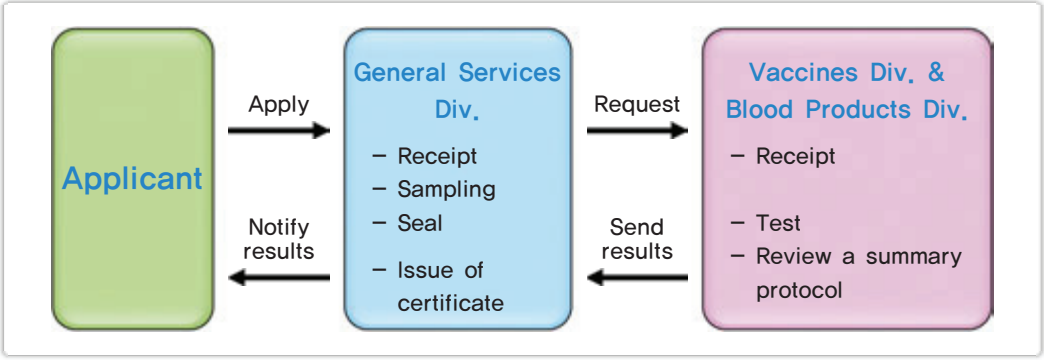

Figure 7. The work flow of national lot release procedure

Both Vaccines Division and Blood Products Division work closely with other divisions in the MFDS and NIFDS. They also cooperate with manufacturers and importers of biologics, WHO, and foreign regulatory authorities such as the European Directorate for the Quality of Medicines & HealthCare (EDQM), the U.S. FDA, and Japan's National Institute of Infectious Diseases (NIID), *etc*.

4 Status of National Lot Release

4.1 Subjects for National Lot Release

As of the end of 2015, subjects for the national lot release included 67 preparations and 195 products.

For bacterial vaccines, subjects for the national lot release are 19 preparations and 39 products. For tuberculin, subject is one preparation and one product. The details are as follows:

Table 1. Bacterial vaccines for national lot release

Preparation
Oral Typhoid Vaccine
Purified Vi Polysaccharide Typhoid Vaccine
Inactivated Oral Cholera Vaccine
Freeze-dried BCG Vaccine for Intradermal Use
Freeze-dried BCG Vaccine for Percutaneous Use
Pneumococcal Polysaccharide Vaccine
Pneumococcus Conjugated to Diphtheria CRM197 Vaccine
Pneumococcal Protein D (NTHi) Conjugate Vaccine
Adsorbed Diphtheria-Tetanus-Acellular Pertussis Combined Vaccine (DTaP Vaccine)
Adsorbed Diphtheria-Tetanus Combined Vaccine for Adult (Td Vaccine)
Adsorbed Diphtheria-Tetanus-Acellular Pertussis Combined Vaccine for Adult (Tdap Vaccine)

Preparation
Adsorbed Diphtheria–Tetanus–Acellular Pertussis–Enhanced Inactivated Poliomyelitis Combined Vaccine (DTaP–IPV Vaccine)
Adsorbed Diphtheria–Tetanus–Whole Cell Pertussis–Hepatitis B (rDNA) Combined Vaccine (DTwP–HepB Vaccine)
Adsorbed Diphtheria–Tetanus–Whole Cell Pertussis–Hepatitis B (rDNA)–*Haemophilus influenzae* type b Conjugated to Diphtheria CRM197 Combined Vaccine (DTwP–HepB–Hib Vaccine)
Adsorbed Diphtheria–Tetanus–Whole Cell Pertussis–Hepatitis B (rDNA)–*Haemophilus influenzae* type b Conjugated to Tetanus Toxoid Combined Vaccine (DTwP–HepB–Hib Vaccine)
Haemophilus influenzae type b Conjugated to Diphtheria CRM197 Vaccine (Aluminum Adjuvanted)
Haemophilus influenzae type b Conjugated to Tetanus Toxoid Vaccine
Meningococcal Group A,C,W135,Y Conjugated to CRM197 Vaccine
Meningococcal (Group A,C,W135,Y) Polysaccharide Conjugated to Diphtheria Toxoid Vaccine

Table 2. Tuberculin preparation for national lot release

Preparation
Tuberculin Purified Protein Derivative (PPD)

For viral vaccines, subjects for the national lot release are 26 preparations and 102 products.

Table 3. Viral vaccines for national lot release

Preparation
Freeze–dried Smallpox Vaccine
Influenza HA Vaccine
Influenza Vaccine (Split Virion, Inactivated)
Influenza Vaccine (Surface Antigen, Inactivated)

Preparation
Cell Culture-derived Influenza Vaccine (Surface Antigen, Inactivated)
Influenza Vaccine (Surface Antigen, Inactivated, MF59C.1 Adjuvanted)
Live Attenuated Influenza Vaccine (Intranasal)
Novel Influenza Vaccine (Split Virion, Inactivated)
Adjuvanted Novel Influenza Vaccine (Split Virion, Inactivated)
Adjuvanted Pre-pandemic Influenza (H5N1) Vaccine (Split Virion, Inactivated)
Adjuvanted Pre-pandemic Influenza (H5N1) Vaccine
Japanese Encephalitis Vaccine
Freeze-dried Cell Culture-derived Japanese Encephalitis Vaccine
Freeze-dried Live Attenuated Japanese Encephalitis Vaccine
Freeze-dried Live Attenuated Japanese Encephalitis Vaccine (rDNA)
Haemorrhagic Fever with Renal Syndrome (HFRS) Vaccine (Inactivated)
Enhanced Inactivated Poliomyelitis Vaccine
Freeze-dried Live Attenuated Measles-Mumps-Rubella Combined Vaccine
Freeze-dried Live Attenuated Measles-Mumps-Rubella-Varicella Combined Vaccine
Hepatitis A Vaccine
Hepatitis B Vaccine (rDNA)
Live Attenuated Varicella Vaccine
Live Attenuated Oral Rotavirus Vaccine
Human Papillomavirus Vaccine (rDNA)
Live Attenuated Yellow Fever Vaccine
Live Zoster Vaccine

For botulinum products, subjects for the national lot release are 3 preparations and 16 products.

Table 4. Botulinum products for national lot release

Preparation
Clostridium botulinum Toxin Type A
Clostridium botulinum Type A Toxin-Haemagglutinin Complex
Clostridium botulinum Toxin Type A (150kDa)

Subjects for the national lot release in plasma-derived products that Blood Products Division controls are 18 preparations and 37 products, and eight of which are human plasma-derived component containing complexes, namely fibrin sealant.

Table 5. Plasma-derived products for national lot release

Preparation
Freeze-dried Human Fibrinogen
Freeze-dried Concentrated Human Blood Coagulation Factor Ⅷ
Freeze-dried Concentrated Human Blood Coagulation Factor Ⅷ (Dry Heat Treated)
Monoclonal Antibody-purified, Freeze-dried Human Blood Coagulation Factor Ⅷ:C
Factor Ⅷ:C Monoclonal Antibody-purified, Freeze-dried Human Blood Coagulation Factor Ⅷ:C
Factor Ⅷ Inhibitor Bypassing Activity Complex
Freeze-dried Human Blood Coagulation Factor Ⅸ Complex
Freeze-dried Concentrated Human Antithrombin Ⅲ
Human Serum Albumin
Human Normal Immunoglobulin
Human Normal Immunoglobulin in Maltose (pH 4.25)
Human Tetanus Immunoglobulin

Preparation
Freeze-dried Human Normal Immunoglobulin with Histamine
Human Hepatitis B Immunoglobulin
Human Hepatitis B Immunoglobulin for Intravenous Administration
Human Varicella Immunoglobulin
Freeze-dried Agkistrodon (Salmusa) Antivenom (Equine)
Fibirin Sealant

In 2015, a total of 8 preparations and 10 products were newly approved (2 preparations and 2 products are bacterial vaccines; 4 preparations and 5 products are viral vaccines; 1 preparation and 2 products are botulinum; 1 preparation and 1 product are plasma-derived products).

Table 6. Newly approved preparations in 2015

Preparation
Oral Cholera Vaccine
Adsorbed Diphtheria-Tetanus-Whole Cell Pertussis-Hepatitis B (rDNA)-*Haemophilus influenzae* type b Conjugated to Diphtheria CRM197 Combined Vaccine (DTwP-HepB-Hib Vaccine)
Clostridium botulinum Toxin Type A
Freeze-dried Live Attenuated Japanese Encephalitis Vaccine (rDNA)
Influenza Vaccine (Split Virion, Inactivated)
Cell Culture-derived Influenza Vaccine (Surface Antigen, Inactivated)
Adjuvanted Pre-pandemic Influenza (H5N1) Vaccine
Human Hepatitis B Immunoglobulin for Intravenous Administration

4.2 Statistics on National Lot Release

In 2015, the total number of biologics released was 2,334 lots; more specifically, 186 lots were for bacterial vaccines, 670 for viral vaccines, 536 for botulinum products, and 942 for plasma-derived products. This number was decreased by 35 lots in comparison to the 2,369 lots of 2014.

Table 7. Number of lots annually released by national lot release

year / prep.	2013	2014	2015
Bacterial Vaccines	327	243	186
Viral Vaccines	668	679	670
Botulinum Products	242	471	536
Plasma-derived Products	1,018	976	942
Total	2,255	2,369	2,334

The number of vaccine lots released is as follows:

Table 8. The number of bacterial vaccine lots released in 2015

Bacterial Vaccine	Lots
Purified Vi Polysaccharide Typhoid Vaccine	2
Freeze-dried BCG Vaccine for Intradermal Use	1
Freeze-dried BCG Vaccine for Percutaneous Use	8
Pneumococcal Polysaccharide Vaccine	8
Pneumococcus Conjugated to Diphtheria CRM197 Vaccine	30
Pneumococcal Protein D (NTHi) Conjugate Vaccine	2
Adsorbed Diphtheria-Tetanus-Acellular Pertussis Combined Vaccine (DTaP Vaccine)	18
Adsorbed Diphtheria-Tetanus Combined Vaccine for Adult (Td Vaccine)	2
Adsorbed Diphtheria-Tetanus-Acellular Pertussis Combined Vaccine for Adult (Tdap Vaccine)	10
Adsorbed Diphtheria-Tetanus-Acellular Pertussis-Enhanced Inactivated Poliomyelitis Combined Vaccine (DTaP-IPV Vaccine)	10
Adsorbed Diphtheria-Tetanus-Whole Cell Pertussis-Hepatitis B (rDNA) -*Haemophilus influenzae* type b Conjugated to Diphtheria CRM197 Combined Vaccine (DTwP-HepB-Hib Vaccine)	66
Adsorbed Diphtheria-Tetanus-Whole Cell Pertussis-Hepatitis B (rDNA) -*Haemophilus influenzae* type b Conjugated to Tetanus Toxoid Combined Vaccine (DTwP-HepB-Hib Vaccine)	12
Haemophilus influenzae type b Conjugated to Diphtheria CRM197 Vaccine (Aluminum Adjuvanted)	5
Haemophilus influenzae type b Conjugated to Tetanus Toxoid Vaccine	3
Meningococcal Group A,C,W135,Y Conjugated to CRM197 Vaccine	4
Meningococcal (Group A,C,W135,Y) Polysaccharide Conjugated to Diphtheria Toxoid Vaccine	2
Oral Cholear Vaccine	1
Tuberculin Purified Protein Derivative (PPD)	2
Total	186

Table 9. The number of viral vaccine lots released in 2015

Viral Vaccine	Lots
Freeze-dried Smallpox Vaccine	4
Influenza HA Vaccine	2
Influenza Vaccine (Split Virion, Inactivated)	175
Influenza Vaccine (Surface Antigen, Inactivated)	5
Cell Culture-derived Influenza Vaccine (Surface Antigen, Inactivated)	26
Japanese Encephalitis Vaccine	16
Freeze-dried Cell Culture-derived Japanese Encephalitis Vaccine	28
Freeze-dried Live Attenuated Japanese Encephalitis Vaccine	8
Freeze-dried Live Attenuated Japanese Encephalitis Vaccine (rDNA)	5
Haemorrhagic Fever with Renal Syndrome (HFRS) Vaccine (Inactivated)	4
Enhanced Inactivated Poliomyelitis Vaccine	6
Freeze-dried Live Attenuated Measles-Mumps-Rubella Combined Vaccine	12
Hepatitis A Vaccine	23
Hepatitis B Vaccine (rDNA)	154
Live Attenuated Varicella Vaccine	142
Live Attenuated Oral Rotavirus Vaccine	12
Human Papillomavirus Vaccine (rDNA)	2
Live Attenuated Yellow Fever Vaccine	2
Live Zoster Vaccine	44
Total	670

Table 10. The number of botulinum product lots released in 2015

Botulinum Product	Lots
Clostridium botulinum Toxin Type A	528
Clostridium botulinum Type A Toxin–Haemagglutinin Complex	7
Clostridium botulinum Toxin Type A (150kDa)	1
Total	536

Of the vaccines applied during 2015, the market shares of domestic and imported vaccines were 65.2% and 34.8%, respectively (based on the number of doses). The products produced from the bulk using domestic technology are considered as domestic products, but the products simply filled from the final bulk that has been imported are considered to be imported.

Table 11. The market share of domestic vaccines in 2015

The market share of domestic vaccines				
Vaccine released (Doses)	Domestic vaccine		Imported vaccine	
	Doses	Share (%)	Doses	Share (%)
43,617,178	28,421,999	65.2	15,195,179	34.8

Nine-hundred forty two six lots of plasma-derived products including human serum albumin are released, and the number of lot released by preparation is as follows:

Table 12. The number of plasma-derived product lots released in 2015

Plasma-derived Product	Lots
Freeze-dried Human Fibrinogen	3
Freeze-dried Concentrated Human Blood Coagulation Factor Ⅷ	0
Freeze-dried Concentrated Human Blood Coagulation Factor Ⅷ (Dry Heat Treated)	43
Monoclonal Antibody-purified, Freeze-dried Human Blood Coagulation Factor Ⅷ:C	0
Factor Ⅷ:C Monoclonal Antibody-purified, Freeze-dried Human Blood Coagulation Factor Ⅷ:C	35
Factor Ⅷ Inhibitor Bypassing Activity Complex	6
Freeze-dried Human Blood Coagulation Factor Ⅸ Complex	10
Freeze-dried Concentrated Human Antithrombin Ⅲ	39
Human Serum Albumin	434
Human Normal Immunoglobulin	2
Human Normal Immunoglobulin in Maltose (pH 4.25)	180
Human Tetanus Immunoglobulin	41
Freeze-dried Human Normal Immunoglobulin with Histamine	6
Human Hepatitis B Immunoglobulin	12
Human Hepatitis B Immunoglobulin for Intravenous Administration	32
Human Varicella Immunoglobulin	3
Freeze-dried Agkistrodon (Salmusa) Antivenom (Equine)	2
Fibirin Sealant	94
Total	942

The national lot release for plasma-derived products decreased a little in 2015 due to the remodeling of the manufacturer's plants, however, swift uptrend is expected due to a steady increase in exports and demand for plasma-derived products.

Table 13. Number of lots annually released plasma-derived products by national lot release

year / prep.	2013	2014	2015
Albumin	450	459	434
Immunoglobulin	319	255	276
Coagulation Factor	97	99	94
Antithrombin Ⅲ, *etc.*	48	52	44
Fibrin Sealant	105	111	94
Total	1,019	976	942

5 Major Activities

Major activities that were undertaken at Vaccines Division and Blood Products Division in 2015 are as follows:

5.1 Domestic Activities

Quality control laboratory network

❍ Vaccine laboratory network (Lab-Net)

'Vaccine Lab-Net' was started by Vaccines Division in March 2011 and as of December 2015, thirteen manufacturers and two quality testing institutions participated in the network, and were vigorously involved in activities such as harmonization and standardization of testing methods, establishment of national biological reference standards, and participating in the proficiency testing program.

Subcommittees of Vaccine Lab-Net and their activities in 2015 are as follows:

Table 14. Lab-Net subcommittees and their activities

Lab-Net Subcommittees	Activity
Steering Committee	– Prepared Vaccine Lab-Net operation plans
DTP Subcommittee	– Conducted a collaborative study on the establishment of the national standard for the potency test of acellular pertussis vaccine
Hib Subcommittee	– Conducted a collaborative study on the improvement of polysaccharide content test (alkaline hydrolysis HPAEC-PAD method) for Hib vaccine and Hib combined vaccine
Varicella Vaccine Subcommittee	– Conducted a collaborative study on the establishment of national standard for live attenuated varicella vaccine
Special Subcommittee for Botulinum	– Discussed the current issue for the alternative test method replacing animal tests
Special Subcommittee for QC manual	– Published the 'Biologics Statistical analysis Manual'

❍ Public-Private Forum on Blood Products Research

Blood Products Division put in place, a ‘Public-Private Forum on Blood Products Research’ to lay the foundation to realize quality assurance and international harmonization of blood products, and to establish the technical support systems for safety management of human plasma for fractionation by strengthening communication and cooperation channels between relevant experts and manufacturers/importers, better identifying domestic/international trends, and enhancing capabilities of those responsible for quality control management jobs.

- Internal-external experts committee

  The committee, composed of 16 internal and 24 external experts, held the Public-Private Forum on Blood Products Research on March 25, 2015. At the forum, they discussed major initiatives regarding blood products including plans to run the forum in 2015 and listened to the suggestions and proposals from manufacturers and importers.

- Technical support and improved communication

  Visiting two domestic manufacturers and two importers and having a time to listen to its difficulties on national lot release, cooperation and communication between public-private has been richly enhanced.

- Seminars and training sessions to strengthen blood products quality control management expertise

  The seminar called 'Smart Blood' that was designed to enhance internal expertise was held at a specific period from April to October in 2015 with the aim of strengthening test methods and expertise for the products responsible and capabilities of those responsible for blood products through speeches of invited external lecturers.

- Blood Products Lab-Net

  Blood products subcommittee conducted a collaborative study with NIFDS and three organizations such as Green Cross Corporation, *etc*. on alternative method for pyrogen test and heparin content testing method for antithrombin Ⅲ products.

❍ Biologics Quality Control Lab-Net workshop

'Biologics Quality Control Lab-Net' workshop was held at Seoul AW Convention Center on November 20, 2015, and attended by 92 relevant internal and external employees and other experts.

This workshop was conducted in three parts. During the '2015 operation conditions of quality control laboratory network (Lab-Net) for biologics and a guest lecture' in the first part, a special lecture was given on the subject of development trend and business prospect of domestic and foreign vaccines. In the second part, a group discussion was held for each area during which people got together by the area of vaccines and blood products to discuss research results and listen to the special guest lecture given by an external speaker in each area. In the last part, a proposed manual for statistical processing of biological potency test and the guidelines for proposed national lot release were introduced, and the 2016 operation plan for quality control laboratory network (Lab-Net) of biologics was presented.

In particular, being jointly proceeded with members in vaccines and blood products fields, this workshop provided an opportunity to broaden the common area of mutual understanding between both members and to share challenges in each field.

Blood Products Field

Vaccines Field

Figure 8. Biologics Quality Control Lab-Net workshop in 2015

Research activities

Research and academic accomplishments that Vaccines Division and Blood Products Division made in 2015 are as follows:

Table 15. List of research projects

Title	Research period
Study on production method of HA antigen standard for pandemic influenza vaccine	2014～2015
The study about free PRP contents assay for *Haemophilus influenzae* gype b polysaccharide	2015
Development of alternative test method of potency and identity for fast release of Smallpox Vaccine	2015
Study on the establishment of reference material for pneumococcal conjugated vaccine	2015～2016
Study on manufacutring of reference material for serological assay of acellular pertussis vaccines	2015～2016
Study for manufacture and establishment of 3rd national standard material for Varicella virus Vaccine	2015～2016
Study on the development of test method for Thrombin generation	2015
Study of and alternative pyrogen test for blood products using monocyte activation test	2015

5.2 International Activities

WHO-related activities

❍ Lot Release Hands-on Training

As part of collaboration activities with the WHO following the designation of the WHO Collaborating Center for biological standardization, Vaccines Division has been managing international training program for vaccine lot release since 2012. In particular, the 4th 'Lot Release Hands-on Training' program was provided for government officials from seven regulatory authorities in Asian and South American countries from November 2 to November 10, 2015.

Figure 9. The 4th Lot Release Hands-on Training program

The training program included 1) Introduction of Korea's national lot release system, 2) Review of summary protocol(case study), 3) Hands-on training regarding Measles-Mumps-Rubella (MMR) vaccine potency and endotoxin test, 4) Monitoring of test results and trend analysis(case study). The 2015 training program, in particular, was operated as

a part of the process to be designated as the WHO's Global Learning Opportunities (GLO) Center. From the positive evaluation results, it was considered that Korea's national lot release system was excellent, strict, and advanced.

❍ Technical Service Agreement (TSA) with WHO

TSA for vaccine testing is signed with internationally-accredited external laboratories to conduct tests commissioned by WHO to assess the quality of vaccines purchased by international organizations including UNICEF. Currently, 12 laboratories in 11 countries are in operation as such.

Vaccines Division was first designated as a testing laboratory by WHO for MMR vaccine in May 2006. In addition, it was commissioned to test three additional vaccines - inactivated JE vaccine, live JE vaccine, and chimeric JE vaccine - in December 2012.

In 2015, appearance testing, potency testing, thermal stability testing, and endotoxin testing were performed on one lot of chimeric JE vaccines, and the test results were submitted to WHO.

The 1st Asia Lab-Net workshop

With the objective of establishing a developmental network among national regulatory laboratories in Asia, a project of Asian national regulatory laboratory network (Asia Lab-Net) has been newly carried forward since 2015. For its first implementation, the 1st Asia Lab-Net Workshop was held for two days between the 7th and 8th of September.

7 regulatory laboratory experts from six countries such as Australia, Japan, India, Indonesia, Taiwan, and Thailand were invited. During the open workshop on the 1st day,

an opportunity was given to share the national lot release system of each country in Asia, while 100 interested parties of domestic manufacturing and importing companies of vaccines and blood products were attending. During the closed session on the 2nd day, an in-depth discussion took place regarding the regulatory function of a lot release in Asia by exchanging perspectives of each country on joint researches such as the development of reference standard, etc. in Asia.

Figure 10. The 1st Asia Lab-Net Workshop

Participation in international proficiency testing scheme (PTS)

EDQM conducts the international proficiency testing scheme (PTS) for physicochemical and biological tests to improve the performance for quality inspection of biologics. Vaccines Division and Blood Products Division who are responsible for national lot release have been participating in PTS every year since 2011 and have been evaluated for the performance of lot release.

The Blood Products Division participated in the international PTS for hepatitis C virus nucleic acid amplification tests (HCV-NAT) hosted by the EDQM in 2015. Of the total 24 participating organizations, 22 test organizations including the Blood Products Division received 'satisfactory' results for the proficiency test.

Currently, as of the end of 2015, the Vaccines Division participated in the international PTS for D-antigen content test which is a potency test of enhanced inactivated polio vaccines and plans to check quality inspection performance at the international level.

Participation in the Experts's Conference

❍ Participation in the 2nd Symposium for Vaccine Quality Control and Research

We participated in the symposium that was held by the National Institute of Infectious Disease (NIID) of Japan to strengthen the cooperation for vaccine quality control and research and introduced the national lot release system of Korea and presented the vaccine research trend. Information about national lot release system of each country, quality control of vaccines, development of vaccines, recent research trend, etc. was exchanged. And the ideas for strengthening the cooperation as a WHO cooperation center were discussed.

❍ Participation in the 16th Vaccine Regulatory Authorities Conference Hosted by WHO

Being invited to the 16th Developing Country Vaccine Regulators' Network (DCVRN) Conference hosted by WHO as the representative of South Korea and as an expert, we suggested our opinions on strengthening the regulatory supervision of regulatory organizations of developing countries in relation to the assessment and permission for development of vaccines and clinical trials. Information was exchanged with the

authorities of regulatory organization of each country, and the international trend was apprehended. Countries such as Brazil, Cuba, India, Indonesia, Iran, South Korea, Thailand, and South Africa and WHO representatives and experts participated in this conference, and discussions about particular diseases and vaccines took place separately for the areas of science and policy.

Other Activities

❍ Conducted a Customized Technology Transfer Training for National Lot Release for Malaysia and Philippines

This year, the training was conducted for five days from September 14th to 18th upon the requests by the Ministry of Health, Malaysia and the Food and Drug Administration, Philippines. Details included 1) introduction of a national lot release system in Korea, 2) summary of BCG and MMR vaccines, introduction of major test items and a field study, and 3) case study of reviewing the summary protocol for production and quality control.

❍ Invitational Training and Lectures to Strengthen Competency of Biopharmaceutical Safety and Regulation Control in Bangladesh

The training was organized by the International Cooperation Office of the Ministry of Food and Drug Safety and was conducted for 15 people from the Directorate General of Drug Administration of Bangladesh (DGDA) on three topics of 1) Evaluation and Approval, 2) GMP, and 3) National Lot Release.

Figure 11. Training for Directorate General of Drug Administration of Bangladesh

❍ Interagency research collaboration with Paul Ehrlich Institute (PEI), Germany

PEI is an institution of the Federal Republic of Germany that carries out the approval of clinical trials and marketing authorization, national lot release, pharmacovigilance, relevant research, *etc.*, in biopharmaceuticals. The MFDS signed an interagency MOU with the PEI in biopharmaceutical areas on October 1, 2013.

Based on the training program for monocyte-activation test (MAT) in PEI, the Blood Products Division established conditions and procedures for *in vitro* alternative pyrogen test method which uses a mononuclear activation test by conducting its own research projects.

❍ Participation in the Conference for ‘Advancement of Risk Analysis-Based National Lot Release System’ upon the Invitation by the European Directorate for the Quality of Medicines (EDQM) and the Agence Nationale de Sécurité du Médicament of France (ANSM)

One person from each of the Biopharmaceutical Quality Management Division, the Vaccines Division, and the Blood Products Division visited EDQM and ANSM to discuss the system operation status and compare operation procedures through a conference with relevant authorities of national lot release in Europe. As a result of this conference, including adjustment of major test items, sample collection methods, and network activities among expert group-manufacturer-regulatory organizations in accordance with future human resources, cost, and international situations, the various mid- and long-term improvements and basis for risk analysis-based national lot release system could be obtained.

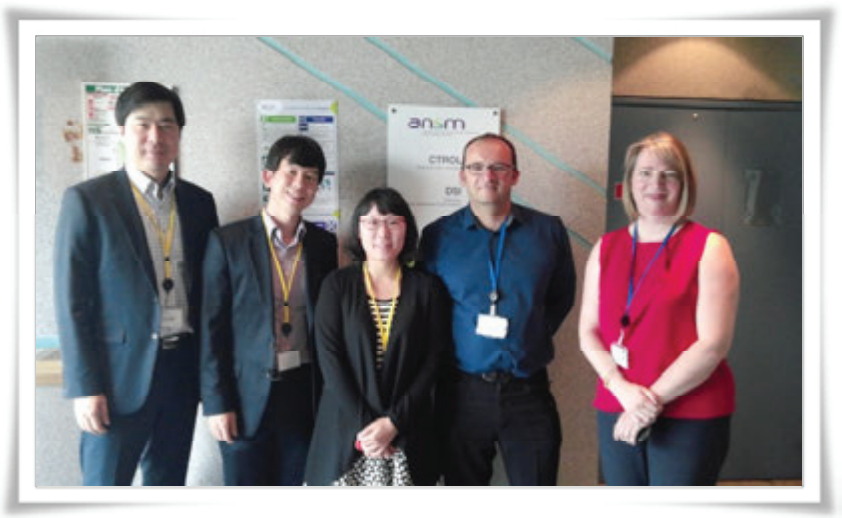

Figure 12. Visit to Agence Nationale de Sécurité du Médicament in France

5.3 Plasma Master File

Support for investigation of blood establishments and review a plasma master file (PMF)

"Enforcement Rule of the Pharmaceutical Affairs Act" was revised in 2012 to unify management criteria for plasma used to manufacture plasma-derived products. The revision made the scope of the management expands to include not only source plasma for domestic products, but also overseas plasma suppliers for imported plasma-derived products and the investigation body changed from Korea Red Cross to the MFDS. In addition, management criteria such as mandatory reporting of PMF[1] and source plasma tests[2] were tightened.

An official from Blood Products Division took part as an investigator in the overseas investigation (including the Central Pennsylvania Blood Bank, U.S. and 4 others) of plasma manufactures and plasma testing laboratories in 2015 by Biopharmaceutical Quality Management Division, MFDS. In addition, checklists were documented to conduct a technical review of the PMFs, and reviewed the initial 5 case reports and 72 periodic reports.

1) PMF : These data cover all aspects of the use of plasma, from collection, storage, and transportation to plasma pool

2) Reinforcement of plasma tests: for EIA, from 5-mini pools to individual plasma; HBV test on NAT became mandatory

5.4 Quality Assurance in National Lot Release Testing

Operation of internationally-accredited testing laboratory (ISO/IEC 17025)

To secure enhanced traceability and international confidence of its test results in line with ISO/IEC 17025 general requirements, the NIFDS has built systematic quality control and quality assurance systems in tests and analyses. As a result, in December 2004, it was recognized as an internationally accredited testing laboratory by Korea Laboratory Accreditation Schemes (KOLAS).

To be an internationally accredited testing laboratory, overall operation and level of confidence are assessed by KOLAS, which is authorized by international accreditation body. As of 2015, Vaccines Division was recognized as an internationally accredited testing laboratory for three preparations and four testing items [bacterial concentration for freeze-dried BCG vaccine for intradermal use, potency test for MMR vaccine, *in vitro* potency test - ECLIA testing method (Ⅰ), (Ⅱ) for hepatitis B vaccine (rDNA)].

To maintain the accreditation as an international accredited testing laboratory, we will conduct an internal evaluation once every year and take a renewal assessment conducted by the KOLAS in August 2016. The Blood Product Division is also preparing a new designation for the test of blood coagulation factors Ⅷ and Ⅸ to increase the ISO17025 accredited test items in 2016.

In addition, the Vaccines Division and the Blood Products Division are continuously making effort to secure reliability by enhancing the work ability of employees, etc. through a training on measurement uncertainty, a practical training for the operation of KS Q ISO/IEC 17025 and participation in the continuing education, and an in-house training every year.

6 Appendix

6.1 National Immunization Program

Expansion of national immunization program (NIP)

Ever since national immunizations against smallpox and cholera began in Korea in 1912, the number of nationally recommended vaccines increased every year. As of December 2015, there are 17 vaccines that are designated and administered under the NIP.

The most recent vaccines added to the NIP in the last three years were Hib vaccine in 2013, pneumococcal vaccine (PCV, PPSV), live attenuated JE vaccine in 2014 and hepatitis A vaccine in 2015. After June of 2016, human papillomavirus vaccine is scheduled to be added to the NIP.

- BCG (Intradermal)
- Hepatitis B (HepB)
- Diphtheria-Tetanus-Pertussis (DTaP)
- Diphtheria-Tetanus for Adult (Td)
- Diphtheria-Tetanus-Pertussis for Adult (TdaP)
- Polio (IPV)
- Diphtheria-Tetanus-Pertussis-Polio (DTaP-IPV)
- *Haemophilus influenzae* type b (Hib)
- Pneumococcal (high risk) (PCV, PPSV)
- Measles-Mumps-Rubella (MMR)

- Varicella (Var)
- Hepatitis A (HepA)
- Japanese Encephalitis (JE, Inactivated)
- Japanese Encephalitis (JE, Live attenuated)
- Influenza (Flu)
- Typhoid (high risk) (ViCPS)
- Haemorrhagic Fever with Renal Syndrome (high risk) (HFRS)

6.2 Related Laws and Regulations

Related laws, regulations and guideline

The national lot release is enforced according to the "Pharmaceutical Affairs Act". The details of the Act are specified in related regulations and notices.

1. Pharmaceutical Affairs Act (Act No. 12450, 2014.3.18)
   - Article 53 (Drugs under national lot release)
2. Rule on the Safety of Pharmaceuticals, *etc.* (Ordinance of the Prime Minister No. 1098, 2014.12.19)
   - Article 63 (Scope of the drugs under national lot release)
   - Article 64 (National lot release application for drugs)
   - Article 65 (Collection of samples, *etc.*)
   - Article 66 (Notification of national lot release, *etc.*)
   - [Appendix 5] The standards for control of human plasma for fractionation
3. Enforcement Rule of the Pharmaceutical Affairs Act (Ordinance of the Ministry of Health and Welfare No. 127, 2012.6.15)
4. Regulation on the Products Approval and Review of Biologics, *etc.* (MFDS Notice No. 2013-193, 2013.7.5)
5. Regulation on the Designation, Approval Procedures, Methods, *etc.* of the Drugs under National Lot Release (MFDS Notice No. 2014-190, 2014.11.27)
6. Minimum Requirements for Biological Products (MFDS Notice No. 2014-71, 2014.2.12)
7. Regulation on Fees Charged of Approval for Pharmaceuticals, *etc.* (MFDS Notice No. 2013-179, 2013.4.29.)

8. Standards for Stability Testing of Pharmaceuticals, *etc*. (MFDS Notice No. 2014-59, 2014.2.12)

9. Regulation on Implementing Validation of Pharmaceuticals, *etc*. (MFDS Notice No. 2014-181, 2014.11.10)

10. Regulation on the Management of Testing Capability (MFDS Notice No. 2014-10, 2014.2.12)

11. Regulation on the Management of Sampling, Issue of Certificate Stamp, and Retaining Samples for the Drugs under National Lot Release, *etc*. (MFDS Established Rule No. 44, 2013.7.31)

12. Regulation on the Judgment of Test Results (MFDS Established Rule No. 9, 2013.4.5)

13. Standards for Operation of Proficiency Testing (Korean Agency for Technology and Standards' Notice No. 2012-0056, 2012.2.17)

14. Guideline on National Lot Release (MFDS Guideline No. B1-2015-017, 2015.12)

International guidelines

1. Guidelines for independent lot release of vaccines by regulatory authorities. WHO TRS No. 978, 2014

2. EC administrative procedure for official control authority batch release. EDQM, 2014

3. Guidelines for national authorities on quality assurance for biological product. WHO TRS No. 822, 1992

2015 Annual Report of National Lot Release

Publication organization : National Institute of Food and Drug Safety Evaluation
Publisher : Yeo-Won Sohn
Publication date : August, 2016
Chief editor : Sang Ja Ban
Editorial board : Chiyoung Ahn, Chulhyun Lee, Myung Hee Kang,
Sun Bo Shim, Kikyung Jung, Joonik Ahn, Kwan Soo Kim,
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Yong Seok Kang, Ji-Hye Kim, Garam Min, Kiwon Han
Contact point : National Institute of Food and Drug Safety Evaluation,
Vaccines Division
Telephone No. : 82-43-719-5410~18, 5430~40
Fax No. : 82-43-719-5400

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국민의 건강과 안전, 환경, 소비자의 이익 및 공정한 경쟁을 침해하는 행위를 말합니다.
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2015
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MINISTRY OF FOOD AND DRUG SAFETY
National Institute
of Food and Drug Safety Evalution

Osong Health Technology Administration Complex, 187, Osongsaengmyeong 2-ro,
Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, 28159, Korea
Tel 82-43-719-5438 Fax 82-43-719-5400