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2018 Annual Report of National Lot Release

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

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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 1,797 employees as of Jan 2018 (589 at the headquarters, 418 at the NIFDS, and 790 at the regional FDA). The headquarters is composed of 1 office (Planning and Coordination), 7 bureaus, and 47 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.

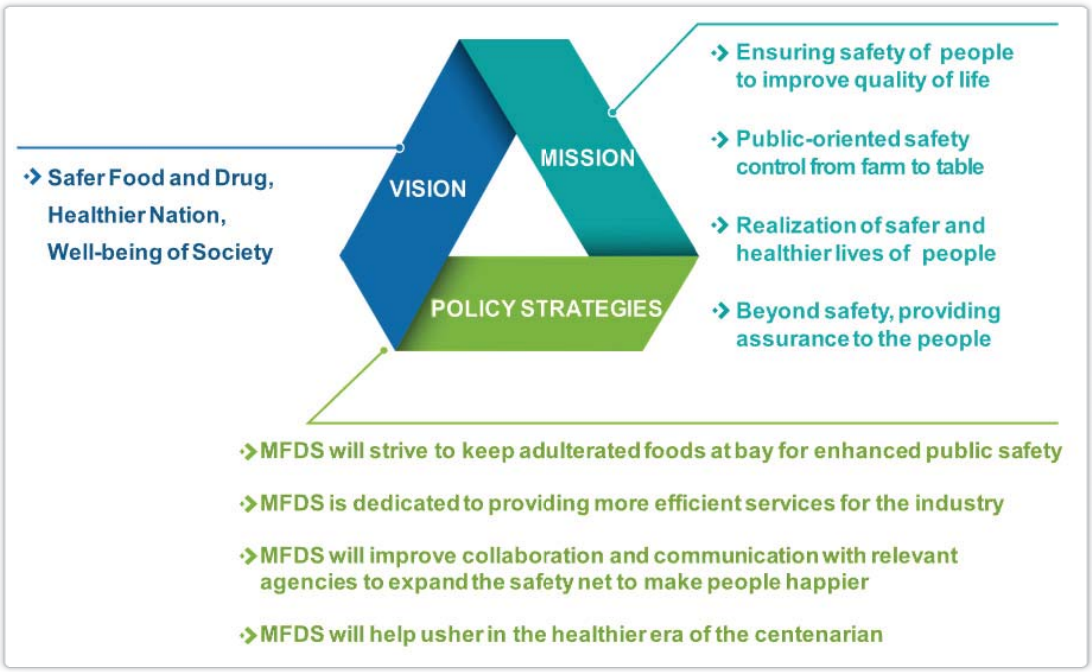

Figure 1. The vision, mission, and policy strategies of MFDS

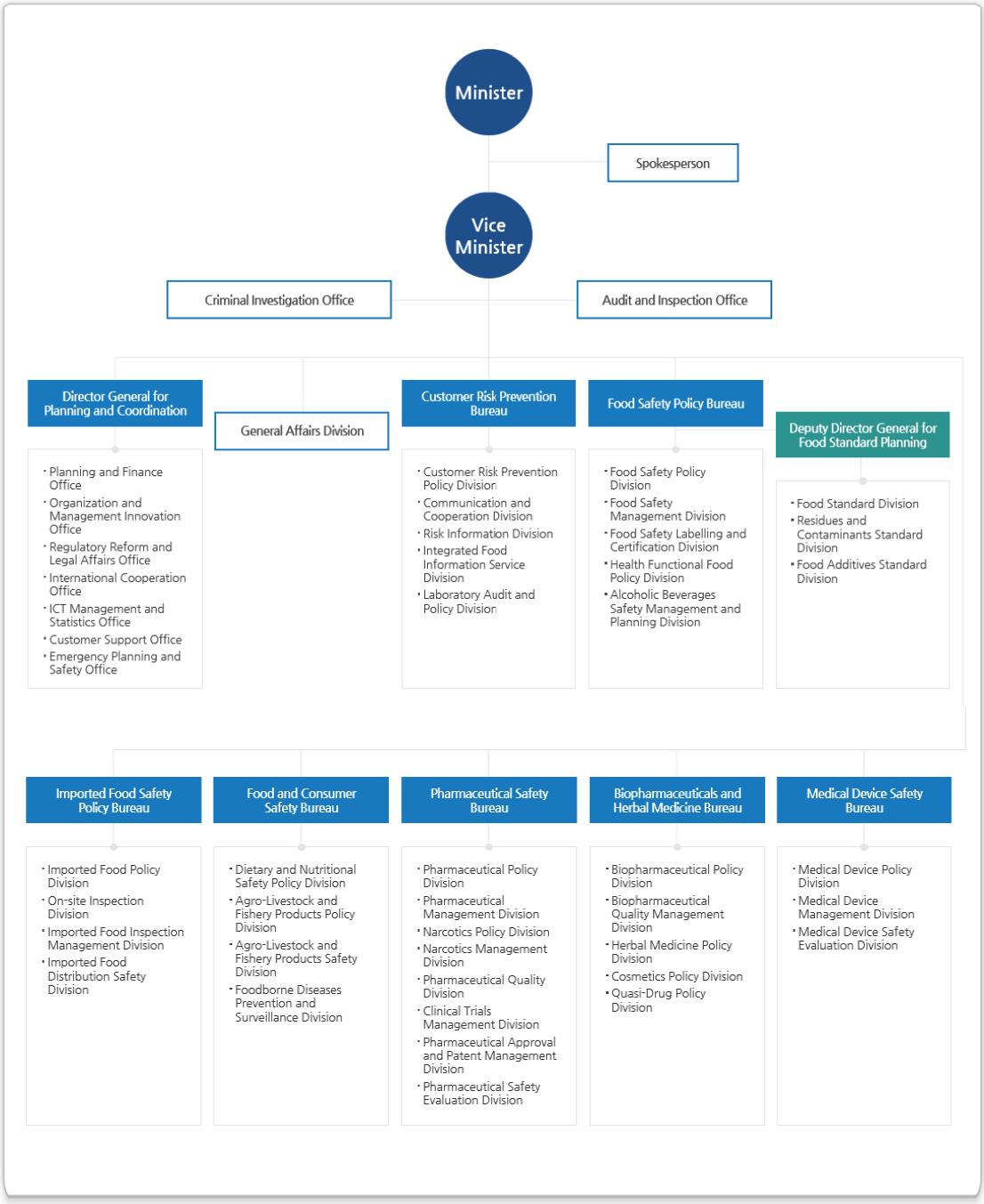

Figure 2. The MFDS headquarters's organization

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, mission, and policy strategies of NIFDS

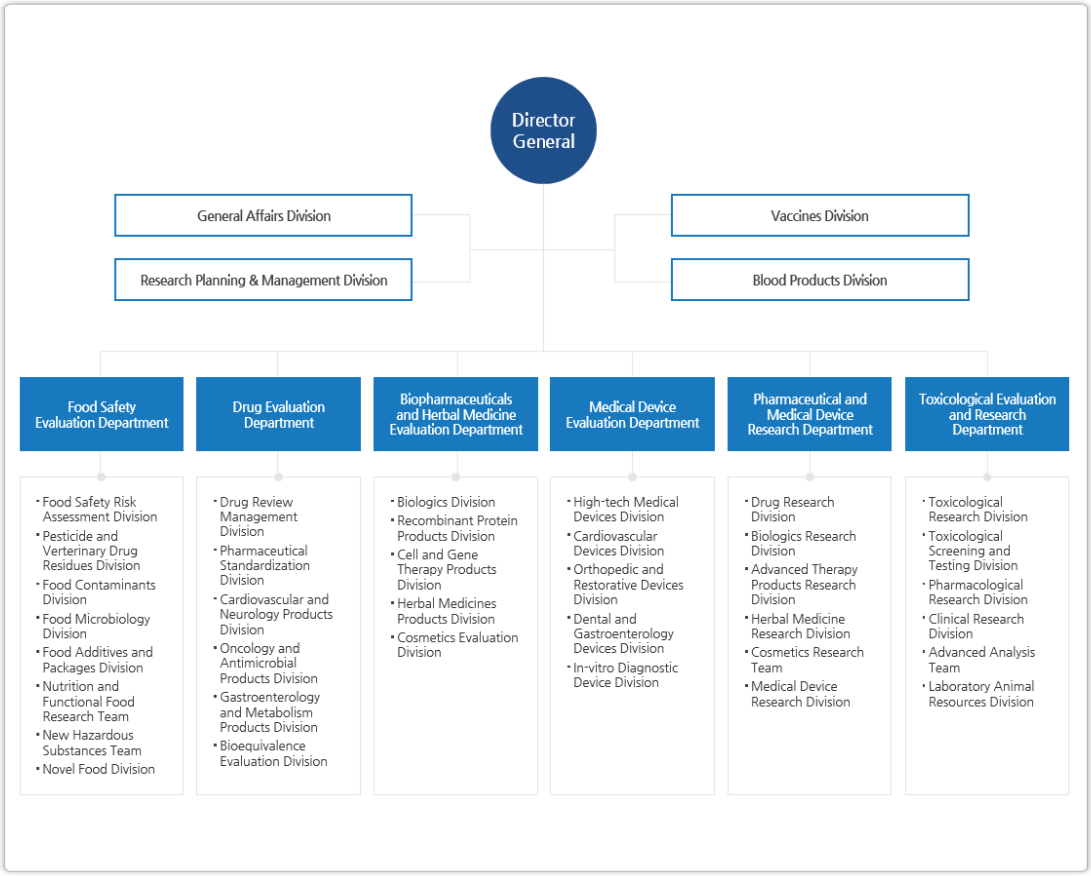

Figure 4. The NIFDS's organization

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.

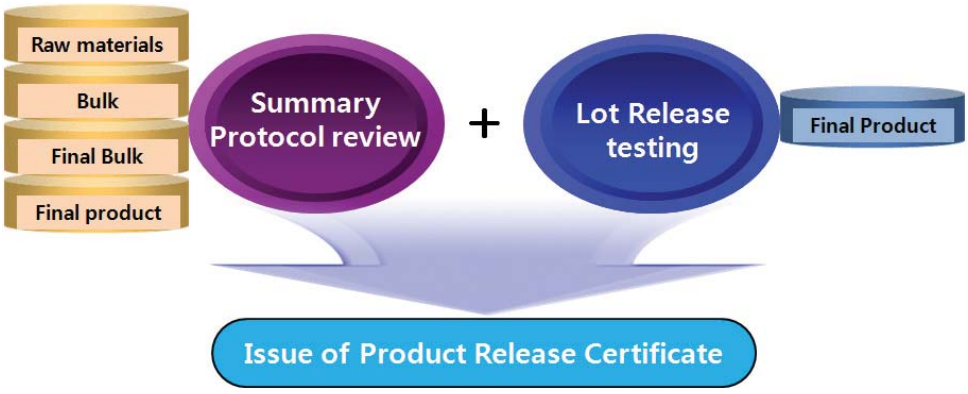

Figure 5. The national lot release system

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. This system has become well-established over the five years that have passed since its first implementation.

In order to operate more advanced model of lot release system, the MFDS has established and run a 'Risk-based Lot Release system' from April 2016. It is the system that the risk attributes of each product are comprehensively reviewed and accordingly the test items are differentiated by the determined risk level of the product. The factors evaluating the risk level of product are as follows: ① history and results of the national lot release, ② history and results of GMP inspections for manufacturing plants, ③ items for approval of products (or revisions), ④ domestic and overseas quality-related safety information etc. In 2018, the risk assessments were conducted for 214 products including 153 vaccine products, 23 botulinum products, 1 tuberculin product and 37 plasma derivatives and antitoxin products. The MFDS has committed to the improvement of national quality control system for the biologics.

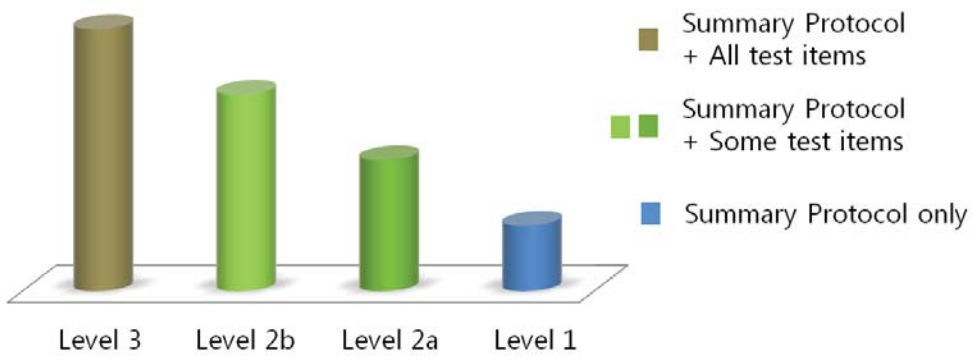

Figure 6. Risk-based Lot Release

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 7 employees and is responsible for plasma-derived products and antitoxins.

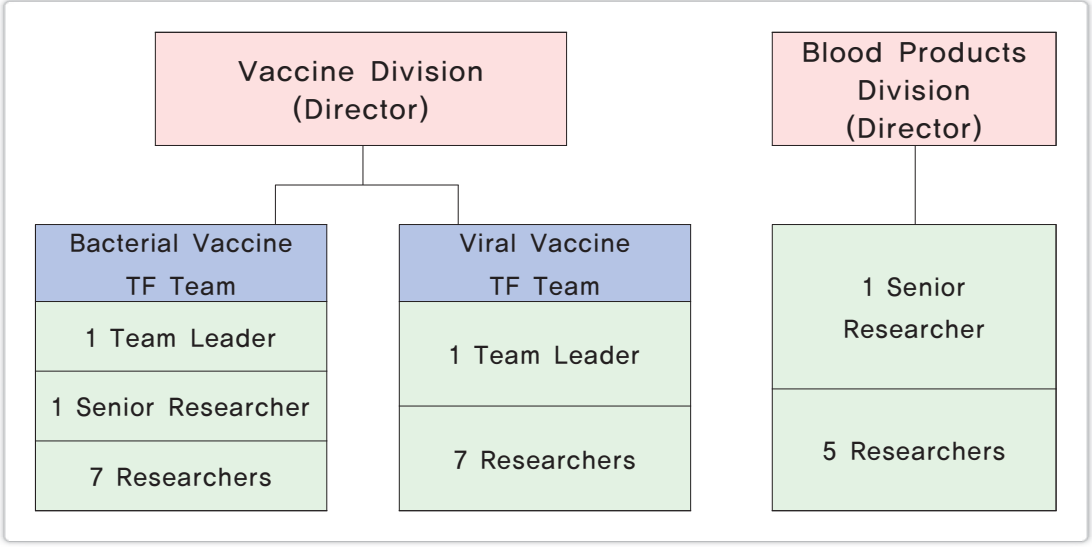

Figure 7. Organizations for national lot release

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:
Starting in 2018, some of the responsibilities of the General Services Division were reassigned to the Vaccines Division and Blood Products Division, which are responsible for the approval of lot release, to perform related tasks more efficiently.

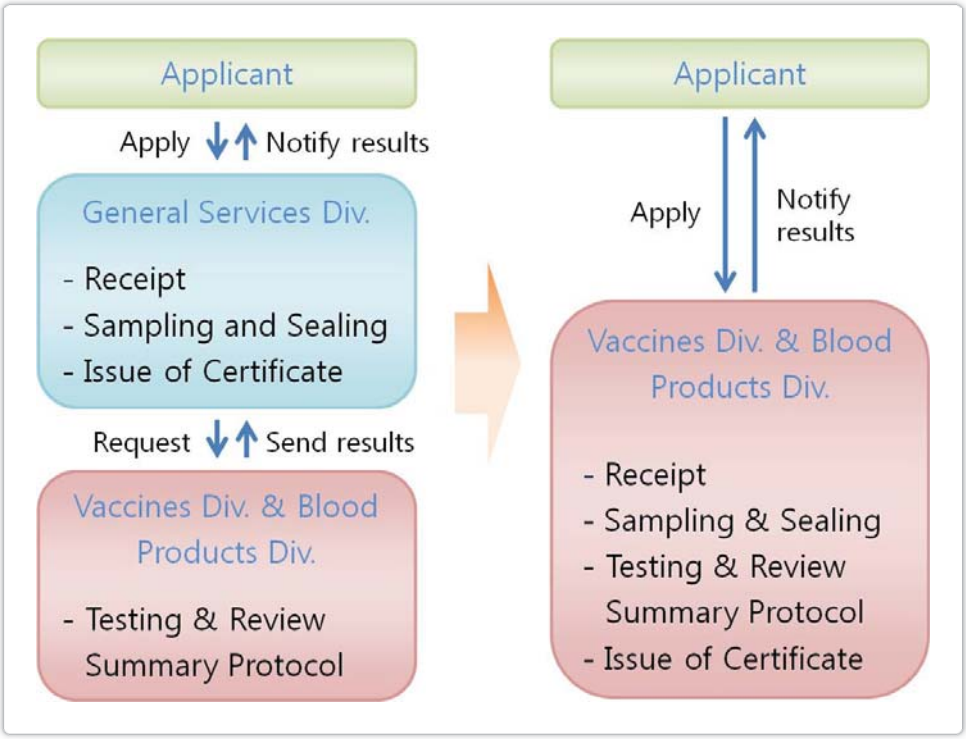

Figure 8. The work flow of national lot release procedure

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, World Health Organization (WHO), and foreign regulatory authorities such as the European Directorate for the Quality of Medicines & HealthCare (EDQM), the Germany Paul-Ehrlich-Institut (PEI), 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 2018, subjects for the national lot release included 67 preparations and 214 products.

For bacterial vaccines, subjects for the national lot release are 20 preparations and 41 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)

Preparation
Adsorbed Diphtheria-Tetanus-Acellular Pertussis Combined Vaccine for Adult (Tdap Vaccine)
Adsorbed Diphtheria-Tetanus-Acellular Pertussis-Enhanced Inactivated Poliomyelitis Combined Vaccine (DTaP-IPV Vaccine)
Adsorbed Diphtheria-Tetanus-Acellular Pertussis-Enhanced Inactivated Poliomyelitis-*Haemophilus influenzae* type b Conjugated to Tetanus Toxoid Combined Vaccine (DTaP-IPV-Hib 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 25 preparations and 112 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)
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)
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

Preparation
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 23 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 seven 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)
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 Normal Immunoglobulin in Glycine (pH 4.8)
Human Tetanus Immunoglobulin
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 2018, a total of 6 preparations and 9 products were newly approved (4 preparations and 7 product are vaccines; 1 preparations and 1 products are botulinum; 1 products is plasma-derived product).

Table 6. Newly approved preparations in 2018

Preparation
Oral Typhoid Vaccine
Adsorbed Diphtheria-Tetanus-Acellular Pertussis-Enhanced Inactivated Poliomyelitis-*Haemophilus influenzae* type b Conjugated to Tetanus Toxoid Combined Vaccine (DTaP-IPV-Hib Vaccine)
Influenza Vaccine (Split Virion, Inactivated)
Live Attenuated Varicella Vaccine
Clostridium botulinum Toxin Type A (150 kDa)
Human Tetanus Immunoglobulin (prefilled syringe)

» 4.2 Statistics on National Lot Release

In 2018, the total number of biologics released was 2,528 lots; more specifically, 248 lots were for bacterial vaccines, 617 for viral vaccines, 545 for botulinum products, and 1,118 for plasma-derived products. This number was increased by 61 lots in comparison to the 2,467 lots of 2017.

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

year / prep.	2016	2017	2018
Bacterial Vaccines	194	265	248
Viral Vaccines	691	654	617
Botulinum Products	597	521	545
Plasma-derived Products	893	1,027	1,118
Total	**2,375**	**2,467**	**2,528**

The number of vaccine lots released is as follows:

Table 8. The number of bacterial vaccine lots released in 2018

Bacterial Vaccine	Lots
Purified Vi Polysaccharide Typhoid Vaccine	3
Freeze-dried BCG Vaccine for Intradermal Use	2
Freeze-dried BCG Vaccine for Percutaneous Use	7
Pneumococcal Polysaccharide Vaccine	9
Pneumococcus Conjugated to Diphtheria CRM197 Vaccine	8
Pneumococcal Protein D (NTHi) Conjugate Vaccine	6
Adsorbed Diphtheria-Tetanus-Acellular Pertussis Combined Vaccine (DTaP Vaccine)	6
Adsorbed Diphtheria-Tetanus Combined Vaccine for Adult (Td Vaccine)	11
Adsorbed Diphtheria-Tetanus-Acellular Pertussis Combined Vaccine for Adult (Tdap Vaccine)	11
Adsorbed Diphtheria-Tetanus-Acellular Pertussis-Enhanced Inactivated Poliomyelitis Combined Vaccine (DTaP-IPV Vaccine)	3
Adsorbed Diphtheria-Tetanus-Acellular Pertussis-Enhanced Inactivated Poliomyelitis-Hepatitis B (rDNA)-*Haemophilus influenzae* type b Conjugated to Tetanus Toxoid Combined Vaccine (DTaP-IPV-Hib Vaccine)	8
Adsorbed Diphtheria-Tetanus-Whole Cell Pertussis-Hepatitis B (rDNA) -*Haemophilus influenzae* type b Conjugated to Tetanus Toxoid Combined Vaccine (DTwP-HepB-Hib Vaccine)	48
Haemophilus influenzae type b Conjugated to Tetanus Toxoid Vaccine	6
Meningococcal Group A,C,W135,Y Conjugated to CRM197 Vaccine	6
Meningococcal Polysaccharide Conjugated to Diphtheria Toxoid Vaccine	4
Oral Cholera Vaccine	109
Tuberculin Purified Protein Derivative (PPD)	1
Total	**248**

Table 9. The number of viral vaccine lots released in 2018

Viral Vaccine	Lots
Freeze-dried Smallpox Vaccine	8
Influenza Vaccine (Split Virion, Inactivated)	233
Cell Culture-derived Influenza Vaccine (Surface Antigen, Inactivated)	38
Japanese Encephalitis Vaccine	2
Freeze-dried Cell Culture-derived Japanese Encephalitis Vaccine	36
Freeze-dried Live Attenuated Japanese Encephalitis Vaccine	2
Freeze-dried Live Attenuated Japanese Encephalitis Vaccine (rDNA)	2
Haemorrhagic Fever with Renal Syndrome (HFRS) Vaccine (Inactivated)	2
Enhanced Inactivated Poliomyelitis Vaccine	4
Freeze-dried Live Attenuated Measles-Mumps-Rubella Combined Vaccine	14
Hepatitis A Vaccine	25
Hepatitis B Vaccine (rDNA)	92
Live Attenuated Varicella Vaccine	66
Live Attenuated Oral Rotavirus Vaccine	4
Human Papillomavirus Vaccine (rDNA)	19
Live Attenuated Yellow Fever Vaccine	3
Live Zoster Vaccine	67
Total	617

Table 10. The number of botulinum product lots released in 2018

Botulinum Product	Lots
Clostridium botulinum Toxin Type A	535
Clostridium botulinum Type A Toxin-Haemagglutinin Complex	1
Clostridium botulinum Toxin Type A (150kDa)	9
Total	545

Of the vaccines applied during 2018, the market shares of domestic and imported vaccines were 58.8% and 41.2%, 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 2018

The market share of domestic vaccines				
Vaccine released (10,000 Doses)	Domestic vaccine		Imported vaccine	
	10,000 Doses	Share (%)	10,000 Doses	Share (%)
5,416	3,186	58.8	2,230	41.2

1,118 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 2018

Plasma-derived Product	Lots
Freeze-dried Human Fibrinogen	5
Freeze-dried Concentrated Human Blood Coagulation Factor Ⅷ	32
Factor Ⅷ:C Monoclonal Antibody-purified, Freeze-dried Human Blood Coagulation Factor Ⅷ:C	42
Factor Ⅷ Inhibitor Bypassing Activity Complex	4
Freeze-dried Human Blood Coagulation Factor Ⅸ Complex	7
Freeze-dried Concentrated Human Antithrombin Ⅲ	58
Human Serum Albumin	435
Human Normal Immunoglobulin	2
Human Normal Immunoglobulin in Maltose (pH 4.25)	235
Human Normal Immunoglobulin in Glycine (pH 4.8)	62
Human Tetanus Immunoglobulin	49
Freeze-dried Human Normal Immunoglobulin with Histamine	10
Human Hepatitis B Immunoglobulin	7
Human Hepatitis B Immunoglobulin for Intravenous Administration	33
Human Varicella Immunoglobulin	3
Freeze-dried Agkistrodon (Salmusa) Antivenom (Equine)	2
Fibirin Sealant	132
Total	**1,118**

5 Major Activities

Major activities that were undertaken at Vaccines Division and Blood Products Division in 2018 are as follows:

5.1 Domestic Activities

Vaccine laboratory network (Lab-Net)

'Vaccine Lab-Net' started in 2011 was 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 2018 are as described in Table 13.

Three subcommittees conducted a variety of activities to improve vaccine quality control, such as collaborative research projects to establish and utilize the national standards as well as assess the proficiency of local manufacturers by the bacterial endotoxin test.

Furthermore, as a part of Biologics Quality Control Lab-Net's activities, MFDS officials, including responsible people from the Vaccines Division, visited Eubiologics' Chuncheon Plant in September 2018. On this visit, the staff looked around the manufacturing facility and received the company's opinion about industrial support, such as the earlier

establishment of Korean national standard vaccines. The MFDS will continue to provide support to companies in the future to ensure self-sufficiency of vaccines in Korea.

Table 13. Lab-Net subcommittees and their activities

Lab-Net Subcommittees	Activity
Steering Committee	- Prepared Vaccine Lab-Net operation plans
Diphtheria vaccine Subcommittee	- Conducted a collaborative study on the establishment of the national standard for Diphtheria anti-toxin
Varicella vaccine Subcommittee	- Conducted a collaborative study on the standardization of the identity test for Varicella and Varicella zoster vaccines
Special Subcommittee for proficiency testing	- Conducted a proficiency testing on the bacterial endotoxin content (Kinetic photometric assay)

Public-Private Collaboration on Blood Products Quality Control

In order to improve the quality control system of blood products through active communication channels between the private and public sectors, the Blood Products Division has operated the Public-Private Forum on Blood Products Research since 2011, in which blood product experts, manufacturers, importers, and blood banks participates.

In 2018, the staff of the NIFDS visited Korean plasma derivatives manufacturers such as SK Plasma, Green Cross, and Korea Red Cross (Plasma Fractionation Center), provided technical support for testing methods, listened to their difficulties, and explored ways to reinforce public-private communication and cooperation.

In addition, in order to establish the national standard of tetanus antitoxin (equine), the Blood Products Division conducted a collaborative research project involving a Korean manufacturer and the K-BIO Health.

Biologics Quality Control Lab-Net workshop

The Vaccines Division and Blood Products Divisions held the Biologics Quality Control Lab-Net Workshop (Lab-Net) on November 14, 2018, in Seoul, which was attended by around 100 vaccine and blood product manufacturers and importers.

The workshop, one of Lab-Net's activities, is a central forum for communication on public-private tasks, and in the 2018 Lab-Net Workshop, 85% of the attendees said Lab-Net activities are important for acquiring expertise or improving research and task abilities. Regarding the quality of presentations like the workshop program, 87% of the participants were satisfied; it was held successfully.

〈Vaccines Field〉

〈Blood Product Field〉

Figure 9. Biologics Quality Control Lab-Net workshop in 2018

Research activities

Research and academic accomplishments that Vaccines Division and Blood Products Division made in 2018 are as follows:

Table 14. List of research projects

Title	Research period
Study on Establishing the 2nd National Standard of Diphtheria anti toxin	2018
Improvement of Polysaccharide content test for meningococcal A,C,W135, Y-CRM197 conjugate vaccine	2017~2018
Study on the Standardization of virus identity test for Varicella and Varicella zoster vaccine	2018
Study to improve of potency test methods for Japanese encephalitis vaccine	2018
Establishment of anti-venom national reference standard for potency test of Freeze-dred Gloydius (Salmusa) antivenom	2018
Study on pyrogen test using monocyte	2017~2018

Domestic proficiency testing program

❍ Bacterial endotoxin test

With a steady increase in the number of vaccines manufactured in Korea, vaccine quality control is becoming increasingly important; thus, in 2018 we assessed proficiency in the bacterial endotoxin method by photometric kinetics, which is performed at many stages during the vaccine manufacturing process. In the proficiency testing program, eight institutions in total participated: the Vaccines Division, a hosting institution, six manufacturers (Green Cross, Boryung Biopharma, SK Biosciences, Ilyang, LG Chem., Korea Vaccine), and the Korea

Pharmaceutical Testing & Research Institute.

Six samples containing international standard (NIBSC code; 10/178) were tested three times. With regard to proficiency, 6 out of the 8 participating institutions showed "Satisfactory" results for the specification (50~200% of target concentration), however one institution revealed "Unsatisfactory" in robust z-score. Accordingly, the NIFDS discussed this matter with the testing institution and identified improvements like SOP revision.

5.2 International Activities

WHO-related activities

❍ WHO Global Learning Opportunities for Vaccine Quality: GLO/VQ

The Vaccines Division ran the Lot release Hands-On Training Program for four years from 2012 to 2015 as a part of cooperation activities as per its designation as a collaborating center by the WHO in the area of biological standardization.

In 2016, building on its past experience and know-how, it was designated for international training in WHO GLO Lot Release/Laboratory Access. In October, 2018, the Vaccines Division provided the training course to ten public servants in charge of vaccine quality control from five countries in Asia region.

Figure 10. 2018 WHO GLO Lot Release/Laboratory Access

The training program mainly includes human papilloma virus vaccine potency testing practice, a case study on the manufacturing and quality control summary review, and a case study on test result monitoring and trend analysis.

WHO GLO training course has produced 56 trainees from 19 countries thus far. Our lot release training course will be shared overseas and should contribute to the improvement of competitiveness in the Korean vaccine industry.

Figure 11. National distribution of trainees completing WHO GLO program

❍ 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, 13 laboratories in 12 countries are in operation as such.

The Vaccines Division was first designated as a WHO's consigned testing organization for MMR vaccines in 2006. It was also designated for three preparations for the Japanese encephalitis vaccines in 2012. The WHO also requested for the BCG vaccines and pertussis vaccine, so by adding pertinent preparations, a total of 7 preparation and 17 test items are in operation in 2018.

Western Pacific Lab-Net Workshop

The Third Meeting of the National Control Laboratories in the Western Pacific Region was held on June 28th 2018 to strengthen cooperative relations among national control laboratories in the region (Figure 12).

The workshop was held in conjunction with the Global Bio Conference (GBC) and attended by quality control experts from regulatory laboratories in countries such as Austria, India, Japan, China, Japan and Vietnam and WHO Western Pacific Regional Office.

Each participating country made a presentation on quality management and safety of immunoglobulin with clinical cases while sharing quality management research results related to blood products and discussing

international collaborative studies to standardize the quality management and testing methods for blood products.

Figure 12. The Western Pacific Lab-Net Workshop

Participation in the Experts's Conference

❍ The Second Meeting of WHO-National Control Laboratory Network for Biologics (WHO-NNB)

The Second meeting of the WHO-National Control Laboratory Network for Biologics (WHO-NNB)' — which was established to share technical information about quality-assured vaccines and to promote mutual recognition of lot-release approval of each country — was held at the CNCF/ISS of Italy with 23 control laboratories and around 50 pharmaceutical experts around the world to share activities of the network and discuss the building of electronic platform.

❍ Conference of the National Institute of Infectious Disease(NIID) of Japan

The NIFDS conducted a collaborative conference with NIID with which National Institute of Food and Drug Safety Evaluation of Korea signed an MOU on the potency assays for Cell Culture-derived Japanese Encephalitis Vaccine in 2017. During the meeting, in-depth discussions on various topics, including local test results, were held for the development of lot release approval system of the two countries.

❍ Participating in Proficiency Testing Scheme (PTS)

- International PTS of the Potency Assays for the MMR Vaccine [administered by the European Directorate for the Quality of Medicines (EDQM)]
- The Third Collaborative Study on the International Standard for Prekallikrein Activator (PKA) Assays [planned by WHO and conducted by the UK's National Institute for Biological Standards and Control (NIBSC)]
- International PTS of the Content Assay for Fibrinogen and Thrombin Concentration in Fibrin Sealants [administered by the European Directorate for the Quality of Medicines (EDQM)]

5.3 Plasma Master File

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

The Enforcement Decree of the Pharmaceutical Affairs Act was amended in 2012 to consolidate the control requirements on raw plasma, which is used to manufacture plasma derivatives. Accordingly, control items were expanded not only to raw plasma in Korean manufacturing items but also to the suppliers of overseas plasma used to manufacture imported items; control requirements were reinforced as reporting the plasma master file (PMF) was made mandatory and raw plasma testing was tightened. As reporting the PMF had made mandatory, 22 initial reports and 74 regular reports from the Korean Red Cross and other organizations were reviewed.

5.4 Quality Assurance in National Lot Release Testing

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

〈 Vaccines 〉

- Cell counting test of Intradermal BCG vaccine
- Viral content test of MMR vaccine
- Potency test of hepatitis B virus (genetic recombination) (ECLIA method(I) and (II)
- Viral content test of Freeze-dried Live Attenuated Japanese Encephalitis vaccine

〈 Blood Products 〉

- Potency test of Dried concentrated human blood-clotting Factor VIII
- Dried concentrated blood-clotting Factor VIII (dried-heating)
- Dried monoclonal antibody purified human blood-clotting Factor VIII:C
- Dried FVIII:C monoclonal antibody purified human blood-clotting Factor VIII:C
- Potency test of Dried human blood-clotting Factor IX complex potency test
- PKA(prekallikrein activator) activity test of human serum albumin
- PKA(prekallikrein activator) activity test of human normal immunoglobulin in maltose(pH 4.25)

- PKA(prekallikrein activator) activity test of human hepatitis B immunoglobulin for intravenous administration
- Potency test of freeze-dried concentrated human antithrombin Ⅲ
- Potency test of human normal immunoglobulin in maltose(pH 4.25)
- Potency test of human normal immunoglobulin, Potency test of human hepatitis B immunoglobulin
- Potency test of human hepatitis B immunoglobulin for intravenous administration
- Identity test for histamine in freeze-dried human normal immunoglobulin with histamine

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 2018, there are 19 vaccines that are designated and administered under the NIP.

The most recent vaccines added to the NIP in the last three years was human papilloma virus vaccine in 2016.

- 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)
- Diphtheria-Tetanus-Pertussis-Polio-Haemophilus influenzae type b (DTaP-IPV/Hib)
- Typhoid (high risk) (ViCPS)
- Haemorrhagic Fever with Renal Syndrome (high risk) (HFRS)
- Human Papillomavirus(HPV)

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 (No. 13598 on December 22, 2015)
   - Article 53 (Biologics under National Lot Release)

2. Rules on the Safety of Pharmaceuticals and Others (Prime Minister Decree No. 1353 on January 4, 2017)
   - Article 63 (Scope of Biologics under National Lot Release)
   - Article 64 (Pharmaceutical Request for National Lot Release)
   - Article 65 (Sampling and Others)
   - Article 66 (Notification of National Lot Release)
   - Article 68 (Label of National Lot Release)
   - [Appendix 5] Raw Plasma Control Requirements

3. Rules on Biologics Designated for National Lot Release and the Release Procedure and Process (MFDS Notice No. 2017-29 on April 28, 2017)
4. Minimum Requirement for Biological Products (MFDS Notice No. 2016-111 on October 4, 2016)

5. Roles on the Control of Sampling and Storage of National Lot Release Pharmaceuticals (MFDS Established Rule No. 92 on January 12, 2017)
6. Rules on the Determination of Testing Results (MFDS Established Rule No. 90 on December 26, 2016)
7. Proficiency Test Operation Standards (Korean Agency for Technology and Standards Notice No. 2015-514 on November 5, 2015)

Guidelines

1. Guideline on National Lot Release. MFDS, 2015
2. Guidelines for independent lot release of vaccines by regulatory authorities. WHO TRS No. 978, 2014
3. EC administrative procedure for official control authority batch release. EDQM, 2014
4. Guidelines for national authorities on quality assurance for biological product. WHO TRS No. 822, 1992

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