Invited Review

Study on the Procedure for Lot Release of Vaccines in Japan

Atsushi Kato^{1*,**} Kentaro Fujita¹, Masaki Ochiai¹, Seishiro Naito¹, and Toshifumi Konda²

¹*Department of Quality Assurance and Radiological Protection, National Institute of Infectious Diseases, Tokyo 208-0011; and* ²*Antimicrobial Resistance Research Center, National Institute of Infectious Diseases, Tokyo 189-0002, Japan*

CONTENTS:

1. Introduction
2. Procedure for lot release in Japan
 - 2-1. History of lot release in Japan
 - 2-2. Organizations involved in regulation of biological products subjected to procedure for lot release in Japan
 - 2-3. Minimum requirements for biological products
 - 2-4. Lot release testing criteria and policy
 - 2-5. Integrating the summary protocol review system into the procedure for lot release in Japan
 - 2-6. Biological products subjected to procedure for lot release
 - 2-7. Application fees, time frames, and complaints towards lot release results
3. Procedure for lot release in different countries and regions
 - 3-1. Study of lot release procedure in other organizations
 - 3-2. Risk based approaches for lot release testing
 - 3-3. Results of the summary protocol review in the procedure for lot release
 - 3-4. Quality risk of vaccines
4. Discussion and conclusion

SUMMARY: Biological products, such as vaccines, blood products, antitoxins, and antivenoms, are released into the market following a lot release conducted by National Regulatory Authorities or National Control Laboratories, even if their manufacturing and marketing have been authorized. Independent lot release by regulatory authorities is not a procedure unique to Japan, but is performed worldwide. Previously, Japan carried out lot release mainly by laboratory tests, and the manufacturers' in-house test records were used as a reference, not involved in the decision of lot release. Conversely, the international standard procedure promoted by the World Health Organization (WHO) includes a document review of the manufacturers' summary protocols, and laboratory tests are listed as an optional procedure. To harmonize with the WHO recommended international method, Japan modified the procedure and introduced a document review in addition to laboratory tests for vaccines in 2012. Since then, substantial knowledge regarding vaccine quality has been obtained during the process of summary protocol reviewing. Here, we outline the current status of the lot release procedure in Japan. We shed light on its history and show recent research based on the knowledge obtained from the protocol review to improve efficiency of laboratory testing and international harmonization.

1. Introduction

Biological products are treated as drugs that require special precautions with respect to public health and sanitation as they are produced from biological materials with relatively little uniformity and their quality, efficacy, and safety are evaluated via biological assays that show some variation in the results. Moreover, vaccines, a representative of biological products, are

usually administered to a large number of healthy people according to a national immunization program. Therefore, governments should ensure their quality via regulatory control. Independent testing by the National Regulatory Authority (NRA) or National Control Laboratory (NCL) in addition to the manufacturers' in-house tests is one of the regulatory approaches used to confirm quality. Japan conducts such a procedure for lot release of every batch of biological products.

Along with globalization of infectious diseases, production and distribution of vaccines against these diseases are being globalized. The World Health Organization (WHO) works actively in the field of public health, establishing uniformity and diversity of vaccines, with international standardization of biological products as one of its approaches (1). To this end, the WHO has been providing global learning opportunities to strengthen NRAs since 1996 (2) and has performed international assessments of NRAs based on WHO vaccine data collection tools (former WHO indicators)

Received October 18, 2018.

J-STAGE Advance Publication November 30, 2018.

DOI: 10.7883/yoken.JJID.2018.446

*Corresponding author: Mailing address: Department of Quality Assurance and Radiological Protection, National Institute of Infectious Diseases, 4-7-1, Gakuen, Musashimurayama, Tokyo 208-0011, Japan.

E-mail: akato@ra2.so-net.ne.jp

**Present address: 237-6 Hakonegasaki, Mizuho-machi, Nishitama-gun, Tokyo 190-1221, Japan.

for regulatory functions since 1997 (3). Moreover, in 2013, the WHO released guidelines for independent lot release of vaccines to circulate recommendations and strategies for lot release of vaccines conducted by NRAs/NCLs (4). These activities are used to strengthen the NRA's functions in vaccine-producing and vaccine-consuming countries at the global level.

Japan previously conducted the procedure for lot release of biological products exclusively by laboratory tests, which were performed by the NCL, and used the record of manufacturers' in-house tests as a reference. After the WHO assessment of the Japanese NRA/NCL in 2011, Japan reformed its legal framework for lot release of vaccines, making it possible to use the record of manufacturers' in-house tests and that of the batch production summary to conform to the WHO guidelines for independent lot release of vaccines (4). In this review paper, we show the procedure for lot release and other relevant regulatory systems in Japan, as well as discuss the necessity of laboratory tests and future procedures for lot releases.

2. Procedure for lot release in Japan

2-1. History of lot release in Japan

Japan has a long history of independent lot release. The lot release procedure for biological products in Japan was enacted in 1915 when medicinal anti-diphtheria and anti-tetanus sera produced by private manufacturers were approved and the criteria for lot release of these products were established (5,6). Medicinal products other than those listed above did not require the NRA/NCL lot release procedure prior to marketing, although manufacturing authorization was required. After World War II, threats to public health by infectious diseases, such as typhus, cholera, smallpox, dysentery, diphtheria, and typhoid fever, increased due to poor hygiene and demobilization (7,8). Many private manufacturers started to produce medicinal products to prevent or treat infectious diseases. Written standards describing the minimum requirements for each product were established as a monograph, and lot release of medicinal products, including vaccines, blood-derived products, in vivo diagnostics, and antibiotics, was initiated in response to instructions from the Public Health and Welfare Section (PHW) of the General Headquarters, the Supreme Commander for the Allied Powers (GHQ/SCAP) to the Japanese Government (9). Two national institutes, the National Hygienic Laboratory (a predecessor of the National Institute of Health Sciences, NIHS) founded in 1874 and the National Institute of Health (a predecessor of the National Institute of Infectious Diseases, NIID) founded in 1947, were responsible for lot release of medicinal products. Roles and responsibilities of these institutes in the procedure for lot release were allocated based on the categories of medicinal products (10–12).

Products that are subject to the procedure for lot release in Japan have been modified many times for various reasons, such as availability of new products, maturation of manufacturing and testing skills, and consistency of product quality, to name a few. Lot release testing was once applied to and omitted from the following medicinal products: antibiotics (until 1985) (13), alternative disinfectants (until 1986) (14),

products for infusion therapy, such as glucose injection (until 1987) (15), contraceptives (until 1986) (16), blood grouping reagents (until 1993) (17), interferons (until 1997) (18), and therapeutic hormones, such as insulin (until 1997) (18). The quality of some of these products is periodically monitored by the NRA of Japan through quality monitoring programs according to the Pharmaceuticals and Medical Devices Act (19). At present, the list of products requiring lot release includes vaccines, most plasma derivatives, antitoxins, and in vivo diagnostics of biological origin. Lot release and the periodic quality monitoring of biological products are conducted by the NIID. For medicinal products other than biological products and antibiotics, periodic quality monitoring is conducted by the NIHS and the prefectural public health institutes. The NIHS, NIID, and prefectural public health institutes are the Official Medicines Control Laboratory (OMCL) of Japan.

Since the 1948 fiscal year (FY), the NIID has conducted lot release for every batch of biological products (Fig. 1). In response to the prevalence of infectious diseases in poor environments of Japan after World War II, the Immunization Act, which made it mandatory for all individuals to be immunized against specified diseases during that time, was enacted in 1948 (20). A large number of vaccine lots were rapidly produced to fulfill the demand. From the mid-1950s, the number of lots increased in accordance with an expansion in species of biological products represented by antibiotics. In 1979 and 1985, the number of lots dropped significantly because oral (21) and parenteral (13) antibiotics, respectively, were excluded from the procedure for lot release in Japan. The exclusion of alternative disinfectants (1986), blood grouping reagents (1993), and interferons (1997) had little effect on the total number of lots because the lot amounts for these products were relatively low compared to the total. The total number of lots was mostly steady in the following 20 years up to the present day (approximately 800–1,200 lots per year), while a gradual decrease in blood products and increase in vaccines was observed.

The pass rates of lot releases were very low at the beginning of lot release from the NIID in the 1948 FY. Approximately 30% of vaccine and/or antitoxin lots were rejected mainly due to sterility failure, while antibiotics showed less sterility problems, and the nonconformance rates of antibiotics were low (less than 10%; data not shown). The nonconformance rate for all products dropped significantly within a couple of years to 0.4%–2.2% (1951–1960 FY) due to an improved sterile manufacturing process, after which it ranged between 0% and 1.2% (since 1961 FY, see Fig. 1 and its upper right window).

2-2. Organizations involved in regulation of biological products subjected to procedure for lot release in Japan

Three organizations are mainly involved in the regulation of biological products (Fig. 2). The Ministry of Health, Labour and Welfare (MHLW) is responsible for making and implementing pharmaceutical policies, regulations, and plans to maintain and improve public health. The Pharmaceutical Safety and Environmental Health Bureau of the MHLW is responsible for most of the regulatory functions for medicinal products, such as

Procedure for Lot Release for Vaccines

Fig. 1. Number of lots and nonconformance rate of independent lot releases conducted by the National Institute of Infectious Diseases (NIID). The number of lots (bar graph, left vertical line) and nonconformance rate (solid line graph, right vertical line) for each category of products in each fiscal year (April 1st to March 31st of the next year, horizontal line) are shown. “Vaccines and others” include prophylactic vaccines, antisera, in vivo diagnostic biological products (e.g., tuberculin and varicella antigen), BCG for intravesical injection, and other biological products that have been subjected to national lot release in the NIID and are not classified in other categories. The upper right window shows an enlarged view of the graph from 1985 to 2017. LR, lot release.

Fig. 2. Organizations and responsibilities of regulatory authorities for biological products subjected to lot release procedure in Japan. Three regulatory organizations for biological products subjected to lot release in Japan are shown schematically. The major functions and responsibilities of each organization are listed. MHLW, Ministry of Health, Labour and Welfare; PMDA, Pharmaceuticals and Medical Devices Agency; NIID, National Institute of Infectious Diseases; GCP, good clinical practice; GMP, good manufacturing practice; GLP, good laboratory practice; GPSP, good post-marketing study practice; AEFI, adverse events following immunization.

licensing, regulatory inspection, establishment of written standards, and supervision of lot release and quality monitoring, while the Health Service Bureau and other bureaus of the MHLW are involved in other regulations, such as the planning of vaccination policies and investigation of adverse events following immunization (AEFI).

The Pharmaceuticals and Medical Devices Agency (PMDA) is one of the Japanese Incorporated Administrative Agencies and was founded in 2004 by reorganizing different organizations originating from the MHLW. The PMDA carries out practical tasks, such as scientific reviews of marketing authorization applications, post-marketing surveillance, good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP), and good post-marketing study practice (GPSP) inspections, and consultations based on entrustment from the MHLW. The PMDA also manages relief compensation for adverse reactions and infections after the administration of pharmaceuticals or biological products, while the MHLW manages the injury compensation program for used vaccines based on the Immunization Act and its amendments (20). The Japanese NRA for medicinal products is thus composed of the MHLW and PMDA.

The NIID is organized as an institution affiliated with the MHLW to scientifically support its administrative function using infectious disease experts and also conducts lot release of biological products as an NCL by utilizing scientific experience and knowledge. As described above, the NIID conducts lot release testing for vaccines and blood products. Blood grouping reagents, antibiotics, and interferons that were omitted from the list of products requiring lot release testing are now occasionally taken from the market and tested by the NIID to monitor quality as a category of the sampling test.

2-3. Minimum requirements for biological products

Written standards describing the minimum requirements for each type of biological product were individually established as monographs from 1949 onwards (22). The minimum requirements for biological products (MRBP) was then established in 1971 (23) as a bundle of product requirements and organized as a compendium for biological products based on Article 42 of the Pharmaceuticals and Medical Devices Act (19 and its amendments). The MRBP has now seen several additions and revisions. In the European Union (EU) and the United States (US), vaccines are listed in the European Pharmacopeia and the US Pharmacopeia, respectively. In Japan, vaccines are specially listed in the MRBP independent of the Japanese Pharmacopeia as described above. The Japanese Pharmacopoeia is published by the PMDA under the authority of the MHLW and has been revised every 5 years since 1971, whereas the periodical revision of MRBP is not ruled.

The MRBP consists of general rules (provisions), monographs, and general tests that include test procedures, measurement reference standards, reagents, buffers, and media. MRBP monographs describe the definitions, summary of manufacturing methods, test methods, specifications, storage conditions, expiry dates, and other requirements for biological products,

such as vaccines, antitoxins, blood products, and in vivo diagnostics for human use. The name of each MRBP monograph reflects the common name of the product, and products released into the Japanese market must comply, as a minimum, with the corresponding monographs of the MRBP.

Generally, a draft of the new monograph is created by the applicant and submitted to the MHLW. If an applicable monograph for the product already exists in the MRBP, the existing one is preferentially applied. Draft monographs are reviewed together with the marketing application during the authorization process, mainly by the PMDA and partly by the NIID, wherein the evaluation results of the pre-approval testing conducted by the NIID to confirm the test methods used by the manufacturers are considered. The draft monograph and the marketing application then undergo public comment and critical review by the Pharmaceutical Affairs and Food Sanitation Council, which is organized by external experts under the secretarial activity of the MHLW as an advisory committee. The draft monograph is finalized by the Pharmaceutical Evaluation Division in the Pharmaceutical Safety and Environmental Health Bureau of the MHLW and is finally published by the MHLW as a ministerial notification concomitantly with the marketing authorization of the corresponding product.

2-4. Lot release testing criteria and policy

Once manufacturing and marketing of biological products are authorized, some tests that are particularly important for product safety and efficacy are selected from the MRBP for lot release testing by the NCL and are posted as the National Assay Standards from MHLW in the Official Gazette. Lot release testing is fundamentally conducted according to methods described in the MRBP. The results of lot release testing are categorized as “pass” or “not pass” following the criterion described in the MRBP. Every lot of product is primarily subjected to a lot release test (100% testing) according to the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act and its amendments (24).

There are some exemptions in the MRBP. Three tests described below can be omitted from the manufacturer’s in-house test and lot release test, if there were no irregularities for certain successive lots in testing the product, and no particular adverse event associated with the vaccines. This tentative period until omission provides an opportunity to confirm any safety issues arising after marketing that were previously not identified in the pre-licensing period. Two of the tests are animal tests using monkeys (neurovirulence tests for rubella and mumps vaccines, and attenuation confirmation test for measles vaccine), which can be omitted once every 5 consecutive lots from the same approved virus strain to meet the requirements. The other test is the abnormal toxicity test for recombinant hepatitis B vaccines, which can be omitted once every 20 consecutive lots to satisfy the requirements.

2-5. Integrating the summary protocol review system into the procedure for lot release in Japan

It is globally recognized that the marketing

authorization process primarily secures vaccine quality, and that the procedure for lot release aims to confirm that the vaccine is produced through an approved process of consistent quality. Therefore, the testing of final products by NCL aims to reconfirm the manufacturer's results. Conversely, it is widely acknowledged that the quality of a vaccine cannot be assured by testing the final product. As an alternative or supportive option, a summary protocol review, in which NRAs/NCLs verify that products are manufactured and quality-controlled for marketing authorization, is promoted by the WHO and now used indispensably for quality assurance of vaccines released into the market (4).

In 2002, the Japanese NRAs for vaccines underwent an assessment by the WHO, which was followed by a follow-up visit in 2004. As a consequence, the WHO strongly recommended the Japanese NRAs to introduce a summary protocol review system. In 2005, the MHLW and NIID created a study group and began introducing a protocol review into the national procedure for lot release of vaccines. Two-step trials of summary protocol reviews were then conducted. In the first step, 4 essential vaccines (BCG, DTaP, measles, and polio vaccines nominated as the expanded program on immunization [EPI]) underwent a trial for one and a half years. In the second step, the objective of applying a trial protocol review was expanded to all prophylactic vaccines, which later underwent a trial for an additional one and a half years. During these trials, the NIID and manufacturers accumulated specific knowledge allowing them to launch the protocol review. Finally, the summary protocol review system was officially implemented in the procedure for lot release of prophylactic vaccines through legal reform in 2012 (25). The summary protocol review was introduced to the final product of the prophylactic vaccines, but was not applied to the bulk vaccine material that requested the NCL's test for quality approval prior to preparing the final bulk product (see section 2-6, i.e. diphtheria [in the form of DTaP or DTaP-IPV], tetanus [in the form of DTaP or DTaP-IPV], measles, rubella, mumps, smallpox, influenza H5N1, inactivated polio [Sabin strain; in the form of DTaP-IPV], and oral polio vaccines).

Currently, only a paper form, and not an electronic form, of the summary protocol is accepted. Moreover, the summary protocols in languages other than Japanese are not accepted in Japan. Information included in the Japanese summary protocols is mostly consistent with the WHO guidelines (4). However, more detailed information on raw materials of animal origin (especially those of ruminant origin) is included in the protocols because of the strict regulations on these materials in Japan (26 and its amendments).

2-6. Biological products subjected to procedure for lot release

Biological products that should be subjected to the national procedure for lot release and their criteria for release (which are named the National Assay Standards) are specified by ministerial notification (27 and its amendments). In Japan, the current procedure for lot release mandatorily applies to vaccines. In some vaccines, such as mumps, rubella, measles, smallpox, and DTaP-based combination vaccines, NCL tests are conducted not only on final products as the lot release

testing, but also on bulk materials as quality approval. Nonconformance lots of bulk materials cannot be used in subsequent manufacturing processes. Generally, several safety tests using animals and cultured cells that take time are specifically categorized within some bulk materials shown above. In 2015, safety tests using small animals, suckling mice, adult mice, and guinea pigs, were omitted from the lot release procedure for bulk materials for measles, rubella, and mumps vaccines. Similarly, those using embryonated hen eggs, primary cells, and continuous cell lines were omitted in 2018.

National Assay Standards given to each vaccine with the same common name in the MRBP can apply to more than one product from the same and/or different manufacturers. It is generally considered that products with the same common name can be used interchangeably to reach the required immunity against the infectious diseases. This interchangeability is useful for administering vaccines to those who require a second or third immunization, since medical staff do not need to check the manufacturer of the first dose vaccine.

Among the vaccines available in Japan, there are 2 exceptions to the standard procedure for lot release. As yellow fever is not prevalent in Japan, the yellow fever vaccine is not distributed commercially. The vaccine is, however, required for travelers who want to travel to the endemic area. It is then purchased by the government and distributed to designated clinics or quarantine stations. Consequently, there is no specification on the yellow fever vaccine in the MRBP, nor in the National Assay Standard. It does not undergo the procedure for lot release, but batch samples undergo a suitable NCL test before distribution. Currently in Japan, H5N1 pandemic influenza vaccines can be exempted from the independent procedure for lot release, but only in the emergent situation where the incidence of pandemic influenza is confirmed and immediate vaccine production and its use are preferred to lot release by the NCL to prevent the spread of the disease (24,28, and their amendments).

2-7. Application fees, time frames, and complaints towards lot release results

Application fees of every product for lot release are defined by the Ministerial Notification by combining the costs of testing and protocol review (27 and its amendments). Marketing Authorization Holders (MAHs) pay the National Treasury for this application. Time frames of every product for lot release are defined as the standard processing periods by the MHLW together with notifications of the respective National Assay Standards and vary depending on the test duration (35–160 days). According to the Pharmaceuticals and Medical Devices Act (19), MAHs have no right to file a complaint against judgment on independent lot release conducted by an NCL. Only the MHLW can make claims concerning the NCL's quality management system, if the MHLW considers it necessary.

MAHs generally apply for lot release only after completing the in-house tests and preparation of documents required for submission. In exceptional circumstances, however, the MHLW allows the NCL to proceed with lot release testing concurrently with the MAH's tests. For example, in the circumstance of a predicted shortage of some vaccine in the market due

to unexpected spread of a disease and where the rapid supply of the vaccine is highly desirable, the MHLW allows the NCL to perform concurrent testing. Judgment of these lot releases by the NCL should be made only after the submission of complete information by the MAH.

3. Procedure for lot release in different countries and regions

3-1. Study of lot release procedure in other organizations

Since globalization of the market for biological products and the wide spread of infectious diseases occur concurrently, it is important to harmonize regulations for these products among different countries and regions to effectively supply them to the public worldwide. To investigate the differences between the Japanese lot release procedure and those in other countries/regions, a study group formed by the NIID and MHLW conducted a questionnaire-based survey during 2013–2016. Nine organizations responsible for lot release of vaccines in vaccine-producing countries or regions, namely Canada, China, EU, Japan, Korea, Taiwan, and 3 other anonymous countries, participated in the survey (29). A summary protocol review was conducted on the procedure for lot release in all of these organizations, but there were differences in the laboratory tests.

All batches were tested (100% testing) in EU, Taiwan, and one of the anonymous countries. However, “100% testing” does not imply that the full set of tests are conducted for every batch as seen in Japan. A system was identified wherein some tests could be omitted for some batches or conducted at reduced frequencies; however, this system is not found in Japan. In the EU, the Official Control Authority Batch Release (OCABR) by an NCL of any given member state was mutually recognized by all member states (30); thus, the burden on an NCL for the lot release of vaccines in EU was relatively lower than that on other NCLs that conduct all the required testing for a country.

Only a fraction of the batches was tested (less than 100% testing) in Canada, China, Korea, and 2 of the anonymous countries. It should be noted that “less than 100%” does not mean that the submitted samples were not assessed at all. There was also a difference among organizations as to whether the appearance inspection was regarded as a so-called test or not. The appearance inspection was conducted on every batch in some of these organizations, even if ordinary laboratory tests were not conducted on the batch.

3-2. Risk based approaches for lot release testing

According to the WHO guidelines, a protocol review is essential for lot release, testing by NCLs is not always necessary, and testing for reduced percentages of lots is acceptable if good consistency is met over a significant period (4). Indeed, Canada, China, Korea, 2 of the anonymous countries in the aforementioned survey, and the US (31) conduct lot release testing at a frequency of less than 100%. Testing frequencies of each product were determined by these organizations using risk assessment based on several factors. While risk calculation information is mostly not disclosed, probably to avoid confusion, the factors considered

for product evaluation in Canada, namely, product indication, nature of the product, production and testing history of manufacturers, information of the summary protocol, testing history of the NCL, inspection history, and post-marketing experience, are open to the public (32).

3-3. Results of the summary protocol review in the procedure for lot release

By introducing a protocol review in 2012, Japan lagged slightly behind other countries in this regard. While the addition of a protocol review to lot release testing by the NIID introduced an additional burden, it provided an opportunity for the NIID to learn about the quality of vaccines, including the consistency of vaccine production and manufacturers’ in-house tests. As a result, this experience cultivated a reliance on vaccine quality. Preparation of the lot protocol also imposed a heavy burden on manufacturing businesses, as there were few approaches from MAHs that complemented some of those from the MHLW and NIID. The possibility of reducing lot release testing was not discussed in exchange for cooperation in standardizing the protocol review.

A study group formed by the NIID and MHLW then investigated the necessity of modifying the procedure for lot releases. Lot release testing has been a useful practice for a long time to ensure the quality, efficacy, and safety of vaccines. This test has worked efficiently when the quality of vaccines was unstable and easily influenced by several factors. Nonconformance batches in the lot release test dropped significantly in the 1951–1960 FY following the improvement of the sterile manufacturing process, when its rates were 0.4%–2.2%. Nowadays, rates have dropped one step further and remain constant at 0%–1.2% (Fig. 1) through the GMP adaptation, indicating that most batches reach a quality that does not require the NCL test in addition to the manufacturers’ in-house test. This was an appropriate time to introduce a lot release procedure that would allow the reduction of the test items from the full test set, as well as reduce the test frequency from 100% to less than 100%. Before introducing this system, it was important to determine how to assess the quality risk of vaccines using the information and experience accumulated from the procedure for lot release. We hereafter define quality risk as the factors obtained from the information, experience, and anything that negatively influenced the quality, efficacy, and safety of vaccines.

3-4. Quality risk of vaccines

As a first approach, the factors required for quality risk assessment of vaccines were designed based on the Canadian system (32). Five factors that could be obtained from the summary protocol and lot release testing were assigned as the hierarchical “level 1” classification, namely “product indication,” “nature of the product,” “production history,” “testing history,” and “protocol review history.” Other important factors for risk assessment, such as inspection history and post-marketing experience, were not included at this time, as they were part of the PMDA’s remit, and information was not routinely shared between PMDA and NIID. Several sub-indicators were then assigned as the hierarchical “level 2” classification. The quality risk of each sub-indicator in “level 2” was scored from

1 to 5 as a simple risk, which were then weighted 0 to 5 depending on the significance of each sub-indicator and how it may influence the quality of vaccines. These scores were assessed by the officers in charge of the procedure for lot release in the NIID. A total of 53 products for vaccines, for which NIID had sufficient experience in laboratory tests and protocol review (Table 1), were thus scored. The weighted score of each sub-indicator was obtained by multiplying the simple risk (1 to 5) and significance (0 to 5), and the overall risk scores were calculated by adding the level 1 scores that were given by the sum of the weighted score of every level 2 sub-indicator.

A histogram of risk scores is shown in Fig. 3. The risk scores of the 53 products (Table 1) were not identical but were distributed within the range of 107 to 283 (mean 230). There was a tendency for the polyvalent vaccines to score higher, while recombinant vaccines and monovalent vaccines with a long history tended to score lower. Interestingly, even in vaccines with the same common name in the MRBP, risk scores of some products varied depending on the manufacturer. From

this result, the introduction of a lot release system that could reduce the test items or frequency depending on the quality risk of each vaccine product was proposed.

4. Discussion and conclusion

Japan has a long history of independent lot release dating back to the early 20th century. Although the products subjected to lot release have changed many times due to changes in availability of new products and the maturation of manufacturing and testing processes, the procedure itself had only changed marginally. A major change, the introduction of a summary protocol review, was made to the lot release procedure in 2012 to harmonize the regulatory system, as recommended by the WHO to every NCL/NRA. The introduction of a protocol review needed considerable discussions among relevant organizations and took several years, resulting in modification of the legal framework. This modification facilitated the Japanese NRA/NCL to improve its regulatory system to an international standard, although it was still behind many countries. As an NCL of Japan, the NIID had ample experience in reviewing summary protocols and therefore, it communicated with other

Table 1. Vaccines applied for the risk analysis

Common name of product ¹⁾	Product number ²⁾
Freeze-dried live attenuated cell culture smallpox vaccine	1
Freeze-dried, cell culture-derived japanese encephalitis vaccine	2
Freeze-dried inactivated tissue culture rabies vaccine	1
Freeze-dried live attenuated varicella vaccine	1
Inactivated poliomyelitis vaccine (salk vaccine)	1
Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio (sabin strains) combined vaccine	2
Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio (salk vaccine) combined vaccine	1
Live attenuated human rotavirus vaccine, oral	1
Rotavirus vaccine, live, oral, pentavalent	1
Freeze-dried inactivated tissue culture hepatitis A vaccine	1
Recombinant adsorbed hepatitis B vaccine (yeast-derived)	3
Freeze-dried live Attenuated measles vaccine	3
Freeze-dried live Attenuated measles and rubella combined vaccine	3
Freeze-dried live Attenuated rubella vaccine	3
Freeze-dried live Attenuated mumps vaccine	2
Pneumococcal vaccine (23-valent)	1
Pneumococcal 13-valent conjugate vaccine (diphtheria CRM ₁₉₇ protein)	1
Tetavalent meningococcal vaccine (diphtheria toxoid conjugate)	1
Haemophilus influenza type b conjugate vaccine	1
Adsorbed diphtheria-tetanus combined toxoid	4
Adsorbed tetanus toxoid	5
Adsorbed diphtheria toxoid for adult use	1
Freeze-dried glutamate BCG vaccine	1
Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from <i>trichoplusia ni</i> cells)	1
Recombinant adsorbed quadrivalent human papillomavirus-like particle vaccine (yeast origin)	1
Influenza HA vaccine	10
	53

¹⁾: Common name of product registered in MRBP are shown. English name is followed by the notation in Interviews Form (IF) of respective vaccines.

²⁾: The numbers of respective products applied for the risk analysis are shown.

Fig. 3. Trial histogram of the quality risk score of vaccines in Japan. Fifty-three vaccine products, of which many batches have undergone protocol review since 2012, are scored. The name of each vaccine product is not shown due to confidentiality. Five major factors, “product indication,” “nature of the product,” “production history,” “testing history,” and “protocol review history,” were classified as hierarchical “level 1.” Several sub-indicators were classified as hierarchical “level 2” under the 5 level 1 factors. Quality risk of each sub-indicator in level 2 was scored and weighted. The overall risk score was calculated by adding level 1 scores given by the sum of the weighted score of every level 2 sub-indicators. The risk scores are plotted as the histogram. Horizontal line indicates the risk score and the vertical line indicates the number of products.

organizations in international meetings. This generated interest in the protocol reviewing system regarding how to assess risk of vaccines and how to use the protocol.

Using the international network, a questionnaire-based survey was created to compare lot release systems for vaccines in 9 organizations. A summary protocol review was considered mandatory, but there was a major difference in the lot release procedure in the testing policy for lot release. In the EU, a member of the OMCLs tested every batch of products according to the product-specific OCABR guidelines (33). Although a 100% testing policy was adopted as in Japan, the EU system could omit specific tests after obtaining results from initial lots derived from new strains or seed lots (29,30). Five out of 9 countries/regions that participated in the questionnaire-based survey used a lot release system that allowed part-time testing. A test-item reduction system and a test-frequency reduction system were based on the evaluation of quality risk of vaccines. The Japanese procedure for lot release using full test items for every batch is a very strict procedure that produces robust qualifying vaccines with maximum possible performance. Flexibility in testing strategy based on a risk-based approach, however, is reasonable considering the cost-benefit and optimized use of NCL resources under conditions where the pass rate of lot release testing has reached 99%. As testing requires a considerable amount of resources, challenges to explore and optimize the limited resources of NCLs are worth examining. Moreover, compared to the uniform full test strategy, a flexible testing strategy can accelerate the efforts of MAHs for manufacturing higher quality products that can be released by reducing test items or reducing test frequency in the lot release. This approach

also aims to provide vaccine users with several benefits, namely, a quick supply of vaccines for the market by reducing testing time and a lower risk vaccine produced by MAHs.

To establish a flexible testing policy for lot release, it is crucial to evaluate the quality risk of vaccines. According to the study group comprising the NIID and MHLW, the factors required for quality risk assessment of vaccines were designed and used preliminarily to score 53 vaccine products (Table 1). This is the first time that the distribution of risk scores of major vaccines used in Japan has been shown (Fig. 3). Each risk score showed a value specific to the product and was distributed within the range of 107 to 283. From this result, the introduction of a lot release system that could reduce the number of test items or test frequency depending on the quality risk of each vaccine product was reasonable. In the trial, scores were evaluated with the information and experience obtained from the NIID. As other information, such as GMP inspection and post-marketing surveillance obtained from the PMDA, MHLW, were not included in the evaluation, further studies are needed. Further collaboration and discussion with organizations from other countries with sufficient experience in analyzing the quality risk of vaccines could also be useful.

Acknowledgments The authors are grateful to the representatives of each organization who answered the questionnaire and for their cooperation in our study. We would also like to thank our colleagues who cooperated in the questionnaire on the quality risk of vaccines and the members of study group in the MHLW and NIID. We specially thank Dr. Haruo Watanabe for his supervision of this study and also thank Ms. Takako Uchida for her help during the preparation of this manuscript. This work was

supported by grants-in-aid for Research on Regulatory Science of Pharmaceuticals and Medical Devices from the Ministry of Health, Labour and Welfare of Japan (H24-Iyaku-Ippan-002 and H27-IyakuA-Ippan-004).

Conflict of interest None to declare.

REFERENCES

1. World Health Organization (WHO). Immunization standards. Vaccine quality. Available at <http://www.who.int/immunization_standards/vaccine_quality/en/>. Accessed October 18, 2018.
2. WHO. Immunization standards. We call it learning. Available at <http://www.who.int/immunization_standards/vaccine_quality/glo_vq_learning/en/>. Accessed October 18, 2018.
3. WHO. Immunization standards. Vaccine Indicators. Available at <http://www.who.int/immunization_standards/national_regulatory_authorities/vaccine_indicators/en/>. Accessed October 18, 2018.
4. WHO. Guidelines for independent lot release of vaccines by regulatory authorities. In: WHO Technical Report Series No. 978, Annex 2, 2013.
5. Imperial Ordinance. No. 181. 1915. Japanese.
6. The Home Ministry, Ministerial Ordinance. No. 12. 1915. Japanese.
7. Tanaka S, Sugita S, Moriyama T, et al. Acute infectious diseases in occupied Japan. J Jpn Soc History Med. 2007; 53: 229-48. Japanese.
8. Medical Affairs Bureau, Ministry of Health and Welfare. A 100-year chronology of the medical system from the viewpoint of hygienic statistics. In: A 100-year history of the medical system, suppl. Tokyo: Gyōsei; 1976. p. 25-35. Japanese.
9. Odaka T. Establishment of National Institute of Health of Japan and Reorganization of the Institute for Infectious Diseases, Imperial University of Tokyo. J Jpn Soc History Med. 1986; 32: 423-68. Japanese.
10. Act for Establishment of the Ministry of Health and Welfare (Act No.151); 1949. Japanese.
11. The Cabinet. Cabinet Order. No. 58; 1947. Japanese.
12. The Ministry of Health, Labour and Welfare (MHLW). Ministerial Notification. No. 187. 1949. Japanese.
13. MHLW. Ministerial Notification. No. 39. 1985. Japanese.
14. The Cabinet. Cabinet Order No. 41; 1986. Japanese.
15. MHLW. Ministerial Notification. No. 98. 1987. Japanese.
16. MHLW. Ministerial Notification. No. 22. 1986. Japanese.
17. MHLW. Ministerial Notification. No. 72. 1993. Japanese.
18. MHLW. Ministerial Notification. No. 51. 1997. Japanese.
19. MHLW. Pharmaceuticals and Medical Devices Act. Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. Act No. 145. 1960. Available at <http://www.japaneselawtranslation.go.jp/law/detail_main?re=&vm=&id=3213>. Accessed February 7. Alternating Japanese-English.
20. MHLW. Immunization Act (Act No. 68). 1948. Available at <http://www.japaneselawtranslation.go.jp/law/detail_main?re=01&vm=&id=2964>. Accessed February 7. Alternating Japanese-English.
21. MHLV. Ministerial Notification. No. 29. 1979. Japanese.
22. MHLV. Ministerial Notification. No. 101. 1949. Japanese.
23. MHLV. Ministerial Notification. No. 263. 1971. Japanese.
24. MHLV. Ministerial Ordinance. No. 1. 1961. Japanese
25. MHLV. Ministerial Ordinance. No. 87. 2011. Japanese
26. MHLV. Ministerial Notification. No. 210. 2003. Japanese.
27. MHLV. Ministerial Notification. No. 279. 1963. Japanese.
28. MHLV. Ministerial Ordinance No. 374. 2008. Japanese.
29. Fujita K, Naito S, Ochiai M, et al. A comparative study on lot release systems for vaccines as of 2016. Jpn J Infect Dis. 2017; 70:565-70.
30. European Directorate for the Quality of Medicines & HealthCare (EDQM). In: EU Administrative Procedure for Official Control Authority Batch Release; 2019.
31. U. S. Food and Drug Administration (FDA). Division of Product Quality. Available at <<http://fda.yorkcast.com/webcast/Play/ca45c6676ef74b4e9aab3515446709401d>>. Accessed October 18, 2018.
32. Government of Canada. Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs. 2005. Available at <https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/gui_sponsors-dir_promoteurs_lot_program-eng.pdf>. Accessed February 7.
33. EDQM. Human OCABER Guidelines. Available at <<http://www.edqm.eu/en/human-ocabr-guidelines>>. Accessed October 18, 2018.