A Comparative Study on the Lot Release Systems for Vaccines as of 2016

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INTRODUCTION

The lot release conducted by the National Regulatory Authorities (NRAs) or National Control Laboratories (NCLs) independently of that performed by the manufacturers is a crucial process to assure the quality of vaccines and other biological products distributed in the market. The World Health Organization (WHO) has developed guidelines for independent lot release of vaccines to provide recommendations and strategies for the lot release of vaccines by the NRAs/NCLs (1). Furthermore, the WHO has provided global learning opportunities to strengthen the NRAs since 1996 (2) and has also conducted an international assessment of the NRAs based on the WHO indicators for regulatory functions since 1997 (3). These activities strengthen the lot release function of NRAs as well as other regulatory functions for vaccines globally. However, variations in the lot release system and other relevant activities were also observed in various countries. Since the market of biological products is rapidly becoming global, harmonization of the system is desirable.

In this study, we conducted a questionnaire-based survey and comparative analysis on the lot release system for vaccines in several countries and regions.

MATERIALS AND METHODS

We conducted a questionnaire-based survey to investigate the differences of independent lot release systems mainly focusing on vaccines among countries/regions. A questionnaire was sent to the 10 organizations that were responsible for lot release of vaccines in 2013–2014.

The questionnaire contained the following items: i) procedures required for the lot release of vaccines; ii) type of lots subjected to lot release (imported vaccines for export only); iii) testing frequencies; iv) test items for measles, seasonal influenza, acellular pertussis, and human papillomavirus vaccines; v) stages to start collaboration/discussion with manufacturers regarding the test methods; vi) specifications/standards used to judge the results of independent testing; vii) presence of a system to disclose the data obtained by the lot release testing to the relevant manufacturers; viii) presence of legal or formal system to disclose the data obtained by the lot release testing to third parties; ix) storage of samples for future reference; and x) products subjected to independent lot release (other than vaccines).

Unclear points, if any, were inquired of the relevant persons of the respective organization. International communications in this investigation were done by contacting relevant organizations individually via e-mail, taking great care to maintain the confidentiality and anonymity. The information was finally updated by the respondents in 2016.

RESULTS

Answers to the questionnaire were obtained from 7 countries and 2 regions, namely, Canada, China, the European Union (EU), Japan, Korea, Taiwan, and 3 other countries (A, B, and C) that provided answers based on the condition of anonymity, however, one organization declined to participate in this survey (summarized in Table 1).

The draft manuscript was sent to all organizations involved in the questionnaire survey. We asked them to
Table 1. Comparison of lot release systems for vaccines among various countries/regions as of 2016\(^\text{1-16}\)

| Test item | Canada | China | EU | Japan | Korea |
|-----------|--------|-------|----|-------|-------|
| | Stage to start collaboration/ discussion with manufacturers regarding test method | Clinical trial stage | Non-clinical trial stage | Clinical trial stage | Clinical trial stage | Clinical trial stage | Clinical trial stage |
| | | Immediately before application | Immediately before application | Immediately before application | Immediately before application | Immediately before application | Immediately before application |
| | | Post-application stage | Post-application stage | Post-application stage | Post-application stage | Post-application stage | Post-application stage |
| | | Post-approval stage | Post-approval stage | Post-approval stage | Post-approval stage | Post-approval stage | Post-approval stage |
| | Release method | Protocol review only | Protocol review only | Protocol review only + testing | Acceptance of EU/OCABR certificate | Protocol review only | Protocol review only (partially) |
| | | Domestic | Domestic | Domestic | Domestic | Domestic | Domestic |
| | | Import | Import | Export | Export | Export | Export |
| | | Export (if requested) | Export (if requested) | Export (if requested) | Export (if requested) | Export (if requested) | Export (if requested) |
| | | Percentage of lot to be tested | <100% | 100% | 100% | 100% | 100% |
| | | % | | | | | |
| | | Measles vaccines | | | | | |
| | | HA content (potency) | HA content (potency) | HA content (potency) | HA content (potency) | HA content (potency) | HA content (potency) |
| | | Endotoxin | Endotoxin | Endotoxin | Endotoxin | Endotoxin | Endotoxin |
| | | General safety | General safety | General safety | General safety | General safety | General safety |
| | | Identity | Identity | Identity | Identity | Identity | Identity |
| | | Sterility | Sterility | Sterility | Sterility | Sterility | Sterility |
| | | Mobility (first 5 monovalent bulks) | Freedom from exogenous viruses (bulks) | Neurovirulence (first 5 bulks) | Freedom from other | Freedom from other |
| | | | | | pH | pH |
| | | Ovalbumin content (partial lots) | | | | | |
| | | Leukopenic toxicity | | | | | |
| | | Thimerosal content (if applicable) | | | | | |
| | | Uniformity of dosage units | | | | | |
| | | Freedom from ether | | | | | |
| | | Residual moisture | | | | | |
| | Test item | Potency (immunogenicity) | Potency (IC challenge) | Potency (immunogenicity; new final bulks) | Potency (IC challenge) |
| | | | | Appearance | HIST |
| | | | | | Endotoxin (new final bulks) |
| | | | | | Identity of each type |
| | | | | | 
| | | | | | General safety |
| | | | | | Sterility |
| | | | | | Endotoxin |
| | | | | | Degree of absorption of each type |
| | | | | | pH |
| | | | | | L1 purity (intermediate stages) |
| | | | | | Intact L1 monomer (intermediate stages) |
| | | | | | Protein content |
| | | | | | Extractable volume |
| | | HIST | Identity | HIST | Endotoxin |
| | | Sterility | Appearance | Sterility | Appearance |
| | | General safety | Appearance | General safety | Identity |
| | | Sterility | General safety | Sterility | Endotoxin |
| | | Endotoxin | General safety | Endotoxin | Degree of absorption of each type |
| | | Sterility | Sterility | Sterility | pH |
| | | Endotoxin | Endotoxin | Endotoxin | Endotoxin |
| | | Degree of absorption of each type | | | |
| | | Sterility | Sterility | Sterility | Sterility |
| | | Endotoxin | Endotoxin | Endotoxin | Endotoxin |
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\(1\) The answers summarized in the table were clarified and updated by the respondents in 2016.

\(2\) The answers were clarified and updated by the respondents in 2016.

\(3\) Data are shared retrospectively, not as part of the release process batch by batch.

\(4\) Test data could be shared with the manufacturer only if requested in specific situations, such as investigation.

\(5\) Test data may be disclosed to regulatory agencies with co-operative organisational arrangements.

\(6\) Test data may be disclosed to third parties with the permission of the relevant manufacturers.
Lot Release Systems for Vaccines

Table 1. Comparison of lot release system of vaccines among various countries/regions as of 2016 (continued)²²

| Test item | Taiwan | country A | country B | country C |
|-----------|--------|-----------|-----------|-----------|
| Inactivation | | | | |
| Potency (EC challenge) | | | | |
| Appearance | | | | |
| HIST | | | | |
| Identity | | | | |
| Endotoxin | | | | |
| Appearance | | | | |
| General safety | | | | |
| Sterility | | | | |
| Protein content | | | | |
| Purity | | | | |
| pH | | | | |
| Residual moisture | | | | |
| Appearance | | | | |
| Potency (in vitro) | | | | |
| Adjuvant content | | | | |
| Identity of each type | | | | |
| Sterility | | | | |
| Pla.jpg | | | | |
| Degree of absorption of each type | | | | |
| pH | | | | |
| Acceptance criteria of test²² | | | | |
| MA dossier | | | | |
| Official compendium | | | | |
| MA dossier | | | | |
| Official compendium | | | | |
| MA dossier | | | | |
| International guidelines | | | | |
| Disclosure of test data to the relevant manufacturers | No | No | Yes²³ | Yes²³ |
| Disclosure of test data to third parties upon request | No | Yes²³ | No | Yes²³ |
| Sample storage | Yes | Yes | Yes | No |
| Type of products for lot release other than vaccines | Botulinum toxin | | | |

²² Countries that declined to be identified by name are shown as country A, B, or C.
²³ Testing can be omitted for certain products. Lots from the same final bulk. Testing can also be omitted for the same final lots with different shipments.
²⁴ No testing is performed for non-prequalified vaccines.
²⁵ Quality of plasma derivatives and other biotherapeutics is checked on initial lots by testing before their release onto the market, which is not regarded as lot release.
²⁶ Anti-sera, including antivenoms, will be subjected to lot release in the near future.
review the contents before finalizing the manuscript for publication, and there were no objections against the publication of this manuscript.

Procedures required for the lot release of vaccines: All countries and regions investigated conducted summary protocol reviews together with the selected testing for the independent lot release of vaccines. However, some countries and regions were also found to practice other procedures, depending on the products. These procedures included protocol review exclusively without testing (Canada) and acceptance of lot release certificates from other regulatory authorities (country B). It should be noted that in the EU, the Official Control Authority Batch Release (OCABR) performed by any given member state was mutually recognized by all member states, which principally means that once the conformity of the lot was confirmed by an official medicines control laboratory (OMCL), a batch release could be achieved by accepting the EU OCABR certificate, and no further lot release testing or protocol review would be conducted (4).

Lot release of imported vaccines and vaccines for export only: All countries and regions conducted independent lot release of the batches used domestically, regardless of whether they had been produced domestically or imported from other countries. In some countries, such as countries A and B, the lot release was also conducted for domestically produced batches to be used exclusively in foreign countries. In Canada, the release was based on Canadian specifications, and other countries might choose to recognize/accept the Canadian certificate. A similar situation existed for the EU batch release certificates, which although were based on the EU specifications, might be recognized elsewhere and were requested by manufacturers for this purpose. China, the EU, Japan, Korea, Taiwan, and country C also confirmed the quality of the batches to be exported, if requested.

Testing frequencies: The WHO allows the NRA/NCL to conduct the lot release tests at reduced frequencies (e.g., <100%) depending on the nature of the product and established experience (1). In the EU, Japan, Taiwan, and country C, all lots were tested (100% testing). The “100% testing” does not necessarily mean that the full set of tests specified to be performed during the lot release should be conducted. Some tests were possibly performed not routinely but occasionally, although every batch underwent at least one test. This means that some tests were conducted at reduced frequencies or only for specific situations. For example, in country C, the appearance test had at least to be performed on every lot, while the other tests were not fully required and performed on <100% of lots, taking into account a comprehensive range of factors related to the quality of each vaccine. Another example is in the case of Taiwan, which usually conducted testing on every lot; however, testing could be omitted if another lot derived from the same final bulk or the same lot with a different shipment had already been approved for the lot release in Taiwan (see footnotes in Table 1). Conversely, some countries (Canada, China, Korea, and countries A and B) tested only a part of the lots (<100% testing), which does not necessarily mean that nothing was checked in the laboratory in the submitted samples. The difference among countries/regions in whether the appearance inspection was considered as the so-called test or not might exist, and the appearance test/inspection might be conducted on every lot even without undergoing ordinary testing.

Test items for representative vaccines: To investigate if there was a difference in the test items applied to the lot release in various countries/regions, the test items for measles, influenza, acellular pertussis, and human papillomavirus vaccines were investigated as representative vaccines. In general, potency tests were highly prioritized regardless of the type of vaccines. With regard to the vaccines investigated, several countries and regions, such as China, Korea, Taiwan, and country B, tended to select sterility tests in a lot release. In addition, these countries/regions and Japan usually performed animal tests to evaluate the safety of the vaccines (Table 1).

Initiation of collaboration or discussion with manufacturers regarding the test methods: Based on the inquiry conducted, many countries and regions had a framework to start collaborations or discussions between NCLs and manufacturers regarding the test methods before applying for a marketing authorization (e.g., clinical trial stage, non-clinical trial stage). Conversely, in Japan and country A, such collaboration/discussion typically started after the application.

Specifications or standards used to judge the results of independent testing: Some countries and regions have official compendia, such as pharmacopoeia, in which specifications of vaccines were also defined. Therefore, whether the acceptance criteria for lot release tests adhere either to those in the official compendia or directly to product-specific marketing authorization dossiers is of interest. Among the countries and regions investigated, Japan exclusively adopted the specifications from the official compendia to judge the results of independent testing, while country C exclusively adopted those in the marketing authorization dossiers. In other countries/regions, the acceptance criteria were set based on either the official compendia or the marketing authorization dossiers (or the international guidelines in the case of Canada and country B), depending on the products. It is important to note that the acceptance criteria outlined in the marketing authorization dossiers in Canada were based on the product-specific characteristics or international standards. It is plausible that the acceptance criteria of tests in the marketing authorization dossiers and/or official compendia in other countries/regions were established based on the relevant international guidelines.

Presence of a system to disclose the data obtained by the lot release testing to the relevant manufacturers: The test results obtained in an NCL are useful for manufacturers submitting the test samples to confirm the quality of their products and test methods. Providing the NCL’s test results promotes transparency and may contribute to building a reliable relationship between the NCL and manufacturers. Canada, the EU, and countries B and C had a system that discloses the test results to the relevant manufacturers, while the other 5 countries/regions did not have the same system. This information might not be disclosed routinely, but might be shared only if requested (see footnotes in Table 1).
Presence of legal or formal systems to disclose the data obtained by the lot release testing to third parties: In the countries and regions investigated, China, Japan, Korea, Taiwan, and country B had no legal or formal system that discloses the lot release test data obtained by the NCLs to the third parties, whereas Canada, the EU, and countries A and C had such a system in place. It should be noted that even if the answer to the question was “Yes”, disclosure could be restricted to other regulatory authorities and/or disclosure to a third party requires permission from the relevant manufacturers (see footnotes in Table 1). Taken together with the answers on the disclosure of test results to the relevant manufacturers, Canada, the EU, and country C were relatively open in terms of data disclosure, whereas China, Japan, Korea, and Taiwan were not.

Storage of samples for future reference: Storage of samples in the NCLs allows for future investigation in case of any doubt on the quality of the batch after its release to the market. In Canada, China, the EU, Korea, Taiwan, and countries A and B, samples that had been submitted to the NRAs/NCLs for independent lot release were systematically retained even after the corresponding lot was released, however, this is not the case in Japan and country C, simply because the exact number of samples needed for testing was submitted by the manufacturers in these countries.

Products subjected to independent lot release other than vaccines: In all the countries investigated, independent lot release was conducted for vaccines. It is of interest to know whether there are differences in products other than vaccines that undergo independent lot release. The lot release of plasma derivatives was conducted in all countries or regions except for countries A and B, while that of anti-sera was conducted in Canada, Japan, Korea, Taiwan, and country C. In some countries, other products, such as biotherapeutics, aside from plasma derivatives and anti-sera (Canada), and in vivo diagnostics (Japan, Korea, Taiwan, and country C) were also subjected to lot release.

DISCUSSION

In this study, a questionnaire-based survey was conducted to compare the lot release systems of vaccines in 7 countries and 2 regions.

The testing policy for the lot release was the major difference in the lot release systems among these countries/regions. In the EU, the 100% testing policy was adopted, and tests performed by OMCLs for each product were specified in a series of product-specific OCABR guidelines (5). However, some specific tests (e.g., purity tests on monovalent bulks of influenza vaccines and genotyping tests on monovalent bulks of live-attenuated influenza vaccines) were omitted after the first several lots derived from new strains or seed lots (6,7; see Table 1). Similarly, in Japan, all tests specified in the ministrational notifications had to be conducted for every lot (8), however, several tests using animals, such as neurovirulence test for measles, rubella, and mumps vaccines and abnormal toxicity test for specific vaccines could be omitted after the prescribed number of consecutive lots had passed the tests, as defined in the Japanese official compendia (9).

According to the WHO guidelines, a protocol review is essential for the lot release, testing by the NCLs is not always necessary, and testing for reduced percentages of lots is acceptable if good consistency is maintained over a significant period (1). In some countries, such as the USA (10), Canada, China, and Korea, <100% of lots were tested. Testing frequencies were determined by the regulatory authorities based on the risk assessment considering the product indication, nature of product, production and testing history, information of the protocol, inspection history, and post-marketing experience. For example, in China, several vaccines were subjected only to protocol review, whereas others were subjected to testing (full testing or part-item testing) in addition to the protocol review (11). Furthermore, test items could be added if the NCL deemed it necessary (11). Similarly, in Canada, vaccines were classified into different evaluation groups, all of which required a protocol review and 2 testing strategies (100% or periodic testing group) (12), whereas some products were released based on a protocol review only. The details of these evaluation groups and factors considered in assigning of products to evaluation groups in Canada were open to the public (12). As described above, the same series of tests assigned to each vaccine were routinely performed for every lot of vaccines in the EU. It should be noted, however, there was a legal framework in the EU, which is called phase 2 testing, to apply the additional test(s) for a transitory period following the changes in the situation of the products, such as significant changes in the manufacturing process of the vaccine (4). This kind of flexibility in testing strategy based on a risk-based approach is reasonable considering the cost-benefit performance and optimized use of NCL resources.

Development of appropriate test methods for quality control of vaccines is crucial to evaluate their quality. Scientific and/or technical inputs by the NCLs are important, especially when developing the novel test methods or when introducing test methods with known difficulties. The stages to start collaboration/discussion on the test methods between the NCLs and manufacturers also varied among the countries investigated (Table 1). If the test methods used by the manufacturers were not ideal for quality control of the products, and such an issue was realized for the first time during the marketing authorization process; it could delay the marketing authorization or market release of these products, since validation/verification of test methods and transfer of those to NCLs, if any, requires a certain amount of time. Therefore, initiating a collaboration/discussion at an early stage before marketing authorization might be ideal.

The lot release is one of the regulatory systems to assure the quality of biological products; the other regulatory systems include marketing authorization, Good Manufacturing Practice (GMP) inspection, and post-marketing surveillance (1). There were countries in which the same organizations are responsible for marketing authorization and lot release (and also other regulatory activities, such as GMP inspection and pharmacovigilance in some countries). Close communications among different regulatory activities allows an establishment of the borderless system in which information
obtained from one regulatory activity is recycled and shared among different regulatory activities to assure the quality of products. If these regulatory activities are conducted in different organizations, the staff with enough knowledge of, and experience in, the other regulatory activities may be necessary in each organization for effective communication and feedback and to function in a synergistic way.

An increasing number of biological products and increasing complexity of testing may burden the NRA/NCL resources, such as human, facility, time, and financial ones. In importing biological products, mutual or multilateral recognition/acceptance of lot release certificates issued from the NRA/NCL of the exporting country is a feasible solution to reduce the burden. However, building such network may be difficult due to the differences in the testing policy, test items and methods of manufacturers and NCLs, contents of summary protocols, and other regulatory requirements for the lot release and/or quality control of the products in various countries. Since testing requires a considerable amount of resources, another way to utilize the limited resources of NCLs is through recognition/acceptance of the test results from other NCLs to avoid repetitive testing on the same lots. The test results especially obtained using a well-harmonized test method may be more easily put into practice. International proficiency and/or collaborative studies in various NCLs may help in establishing mutual confidence in the NCLs’ test results and facilitate recognition/acceptance of the test results from other NCLs. Additional testing in the importing country may be necessary if the test methods of the producing country’s NCL is different from those of the importing country or if the testing policy of the producing country is unacceptable in the releasing countries (e.g., a < 100% testing policy in the producing country, with a 100% testing policy in the importing country). Through various activities (e.g., establishing guidelines, conducting assessment of national regulatory systems in each country, holding workshops, providing training, and building regional networks), the WHO tries to promote regulatory harmonization/convergence and information sharing among NRAs/NCLs. Such regulatory harmonization/convergence and close communication among NRAs/NCLs are the key issues to fulfill the mutual or multilateral recognition/acceptance of the lot release certificate and/or test results from other NCLs.

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**Conflict of interest** None to declare.

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