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Meeting Report

The 2nd Meeting of National Control Laboratories for Vaccines and Biologicals in the Western Pacific

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ABSTRACT

The Second Meeting of the National Control Laboratories for Vaccines and Biologicals in the Western Pacific, was jointly organized by the National Institute of Food and Drug Safety Evaluation of the Ministry of Food and Drug Safety in the Republic of Korea, and by the World Health Organization Regional Office for the Western Pacific.

In the National Lot Release Systems session countries including Canada, China, Japan, Malaysia, Vietnam, and the Republic of Korea, all shared information on their current Lot Release Systems, including current practices and developments in risk-based official lot release of vaccines.

In the session on Quality Control of Blood Products, experts from the National Institute for Biological Standards and Control shared quality control and research results for; blood coagulation factor VIII products, and the measurement of procoagulant activity in immunoglobulin products. Representatives from Japan proposed a regional collaborative study to test aggregated immunoglobulin free from complement activity. A cell-based Japanese encephalitis vaccine potency assay was proposed by representatives from Korea and they also called for voluntary participation of other National Control Laboratories in a collaborative study, on the first Korean *Gloydius* anti-venom standard. Participants agreed in general to continue communicating, and coordinate presentation of the study results.

Introduction

The National Control Laboratories (NCLs) play an essential role in the quality assurance for vaccines, blood products and other biological medical products. NCL establish and manage national reference standards, develop and identify models of standard methodology, they review manufacturers' data, and perform independent quality control testing.

Regulatory harmonization through standardization of quality assessment and testing methodology is crucially important for improving access on a regional and global scale. The World Health Organization (WHO) has played an important role in this field through the Expert Committee on Biological Standardization since 1947. The increased speed of development of information technology and biotechnology has become unprecedented, and keeping up with global harmonization of biological norms and standards is increasingly challenging. As a result, policies, strategies

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and standards used by NCLs for quality assurance and quality control of biological products has become divergent. This therefore necessitates the need to promote regional networking based on commonality of regulatory policies and strategies, existence of market or demand on a particular class of products, existence of domestic biological research and production, and developmental history of manufacturers and control laboratories for each country. A continued exchange of information and sharing of good practices across NCLs is an important mechanism to collectively address these challenges.

The second meeting of the NCLs for vaccines and biologicals in the Western Pacific was held on 20-21 September 2017, in Seoul, the Republic of Korea. The objectives of the meeting were as follows: 1) to share information on current Lot Release Systems and Quality Control Research, 2) to review the planning and progress of collaborative studies on measurement methods for the procoagulant activity of immunoglobulin products, 3) to plan collaborative studies, and 4) to exchange views on the need for collaborative NCL activities and priorities.

This report provides highlights of the presentations along with summaries of the discussions that followed, together with conclusions and recommendations for each of the key areas reviewed at this conference.

Participants

The 2-day meeting was organized by the National Institute of Food and Drug Safety Evaluation (NIFDS) and the Ministry of Food and Drug Safety (MFDS) and was co-sponsored by the WHO Regional Office for the Western Pacific (WPRO). This meeting was attended by 110 participants.

Representing the NCLs of 7 countries NIFDS were 1) the Republic of Korea represented by the National Institutes for Food and Drug Control (NIFDC); 2) China represented by the National Institute of Infectious Diseases (NIID), 3) Japan represented by the National Institute for Control of Vaccines and Biologicals (NICVB), 4) Vietnam represented by the National Pharmaceutical Regulatory Agency (NPRA), 5) Malaysia, 6) Canada represented by Health Canada, and 7) United Kingdom represented by the National Institute for Biological Standards and Control (NIBSC).

Quality control laboratories from 4 manufacturers attended: 1) Research Institute for Tropical Medicine (RITM) from the Philippines, and from the Republic of Korea 2) Green Cross, 3) SK Plasma, and 4) Korean Red Cross Plasma Fractionation Center.

The WHO and 3 academic institutions were represented: 1) Korea Hemophilia Foundation, 2) Seoul National University Hospital, and 3) Sookmyung Women's University, the Republic of Korea.

Presentations

Session A: Sharing the lot release system amongst the NCLs

Dr. Irene Lisovsky (Health Canada, Canada) described the current risk-based approach of the Lot Release System in Canada. The monitoring of biologics to verify compliance with established safety and potency profiles, is a key priority of the Biologics and Genetic Therapies Directorate (BGTD) of Health Canada. Health Canada has a risk-based approach Lot Release Program, which is an integral part of the regulatory framework for biologics covering both the pre- and post-marketing stage of a drug's life cycle. Each product is assigned to 1 of 4 evaluation groups; each group with a different level of regulatory oversight based on the degree of risk associated with the product [1]. This graduated risk-based approach to lot testing and oversight allows BGTD to focus on product testing that requires enhanced surveillance (e.g., vaccines and blood products). The considerations used to determine the appropriate evaluation group were the nature of the product; inspection history, testing history, post-market experience and, inclusion of the changes to the manufacturing process. Lot release activities are reviewed on an ongoing basis, and the level of product oversight may change based on benefit/risk considerations, resulting in the movement of a product to a different evaluation group. In addition, Dr. Lisovsky presented a specific case study highlighting how these benefit/risk considerations can be applied to decision making to change the level of oversight for a specific product under the lot release program.

Dr. Chulhyun Lee (NIFDS, Republic of Korea) outlined the current risk-based national Lot Release System in the Republic of Korea. He reported that the MFDS revised the "Regulations on the Designation, Approval Procedure, and Method of Biological Products Subject to National Lot Release" effective on April 1, 2016. The major improvement focused on the risk classification of each product based on risk analysis, thus enabling the system to apply different test items for the lot release of each product, depending on the level of risk. This approach replaces the previous method of examining all test items for each product and then exempting some test items according to the national lot release performance results. The factors related to the overall risk assessment were the history and outcomes of national lot release; the history and outcomes of Good Manufacturing Practice (GMP) inspection for each drug manufacturer, the safety information related to the quality of biologicals at home and abroad, the product license approval (or change) related to the manufacture and quality of biologicals, and other safety information where a review by the

minister of MFDS is deemed to be necessary. The manufacturer will be informed in writing of the assessment results for each product every year. The products that consistently maintains good quality can be exempted from lot release testing, and the national lot release can then be completed within 20 calendar days by reviewing only the summary protocol of the products, which includes the test report of the manufacturer (importer).

Dr. Qiang Ye (NIFDC, China) provided an overview of the Lot Release System in China. Currently, the Chinese vaccine industry output is approximately 2 billion USD, of which the expanded program on immunization (EPI) vaccines account for approximately 15%, whereas non-EPI vaccines account for 85%. In 2016, NIFDC quality tested almost 4,000 lots from 55 categories of vaccines, produced by 41 manufacturers which accounted for approximately one billion doses.

Dr. Ye also suggested that the lot release of products should be conducted based on 3 modes; 1) review of the summary lot protocol only, 2) review of the summary lot protocol and selected testing of samples, and 3) review of the summary lot protocol and full testing of samples.

The main testing items for vaccines are virus titer, identity, potency, content, abnormal toxicity and sterility. Vaccine types, test items and test frequencies are clearly defined in, "Notice about the Implementation of Lot Release of Vaccine Products for Prophylaxis" (No 2047 of ZJS [2005]). Following data accumulation, the frequency of testing for lot release was adjusted by, "Notice of Changes in the Test Items of Various Products and Test Frequency in Laboratory Lot Release" (No 53 of ZJSH [2012]). He also stated that each vaccine has a specific summary review checklist that includes critical parameters such as inactivation time, production method, and quality control testing methods. As a provision to protect public health, vaccines used to control diseases in emergency cases can be subject to exemption from lot release upon CFDA approval. Vaccines donated by UN agencies or other international organizations can also be subject to exemption from lot release upon CFDA approval.

Dr. Masaki Ochiai (NIID, Japan) presented the current status of the Lot Release System in Japan. He stated that the NIID has conducted lot release of biologicals such as vaccines and blood products since 1947. The decision regarding whether a lot can be released had been in principle, based only on the test results performed by NIID, using manufacturers' test results only for reference. In 2012, Japan established a system in which manufacturers' batch records were reviewed as summary lot protocols in the lot release process for vaccines; according to the WHO lot release guidelines for vaccines. NIID obtains critical and significant information such as production records, and the results of tests performed by manufacturers at various stages of production for the batch review of vaccines. The information accumulated in the review process is very useful for assessing the degree of quality risk associated with the product. Under the current rules, every lot of vaccines is subject to lot release testing by NIID, along with the protocol review. Dr. Ochiai stated that NIID is discussing the introduction of a graduated risk-based approach to lot release testing to achieve a more appropriate and efficient use of limited resources, whilst ensuring high quality vaccine.

Session B: Quality control testing methods for Japanese encephalitis vaccines

Dr. Chang Kweng Lim (NIID, Japan) presented an overview of Japanese encephalitis (JE), the quality control for JE vaccines, and the national epidemiological surveillance in Japan. He explained that no specific treatment for JE exists; and vaccination is an effective means of prevention [2]. JE outbreaks in Japan up to 1965, frequently produced 3,000 to 5,000 cases.

The Nakayama strain of the JE virus was first isolated from infected humans in Japan in 1935, and in 1954, mouse brain-derived, inactivated JE vaccine was licensed (Nakayama strain). During the period from 1967 to 1975, a JE vaccine campaign was introduce and the number of JE cases decreased drastically; around 100 JE cases in total were reported between 1972 to 1991, and less than 10 cases have been reported since 1992. Vero cell-derived inactivated JE vaccine was introduced (Beijin-1 strain) in 2009. The quality of the JE vaccine is tested for potency using the 50% plaque reduction neutralization test ($PRNT_{50}$). Briefly, mice are intraperitoneally immunized twice with the vaccine at 7-day intervals, and bled from the heart 1-week post immunization. The neutralizing antibody titer is measured with the $PRNT_{50}$ assay. Potency test results are analyzed by the parallel line assay method using the national reference vaccine. The potency test of the Vero cell-derived inactivated JE vaccine uses a Japanese national reference which was established to satisfy a previous potency standard for the mouse brain-derived reference vaccine and has been made available from the NIID to international NCLs.

In order to evaluate the distribution of JE virus in Japan, national epidemiological surveillance has been performed every year since 1965, including surveillance of the prevalence of hemagglutination inhibition (HI) antibody among domestic swine. There is a good correlation between the emergence of JE cases and HI-antibody positive rates among swine. The JE naïve domestic swine is an important amplifier of JE virus, and the anti-JE virus HI antibody level of swine is a good indicator of JE virus risk.

Dr. Ji Young Hong (NIFDS, the Republic of Korea) reported on the necessity for improved potency testing methods for Vero cell-derived JE vaccines. She stated that until quite recently mouse brain derived JE vaccine was the primary JE vaccine used internationally, although it is increasingly being

replaced by Vero cell-derived JE vaccine. The Vero cell-derived JE vaccine has been licensed for routine use in Korea since 2015. She explained that the quality control of JE vaccines is based on the WHO recommendations and that vaccine potency can be determined by an in vivo PRNT. However, the use of laboratory animal testing has decreased worldwide, following the principle of the replacement, reduction, or refinement of animals. The MFDS developed an in vitro enzyme-linked immunosorbent assay (ELISA) potency test for the mouse brain-derived JE vaccine (Nakayama strain) in 2012 [3]. The MFDS plans to develop an in vitro ELISA potency assay for the national lot release testing of the Vero cell-derived JE vaccine.

Session C: Plasma-derived blood products

Dr. Sanj Raut (NIBSC, the United Kingdom) presented an overview of quality control (Official Control Authority Batch Release, [OCABR]) procedures at NIBSC for batch release of human blood coagulation factor VIII (FVIII) products, with a European perspective.

FVIII products, used in the prevention and treatment of hemorrhage in patients with hemophilia A, are assessed using the chromogenic FVIII potency assay, which is the European Pharmacopoeia (Ph. Eur.) recommended method. Briefly, the assays are carried out on plasma derived FVIII products using standard references from Ph. Eur.; prior to lot release by the manufacturers in OCABR, and potency testing is carried out by Official Medicines Control Laboratories (OMCLs). The Ph. Eur. quality control acceptance criteria for FVIII is "80% to 120% of the labeled potency value." Despite the availability and increase in the use of recombinant FVIII products in Europe, NIBSC has been experiencing a steady increase (~ 7-fold) in the number of plasma derived FVIII batches submitted for OCABR testing over the last decade.

Dr. Raut also highlighted assay discrepancy issues when using different chromogenic assay kits, and these issues were investigated in a European Collaborative Study carried out by the European Directorate for the Quality of Medicines (EDQM). The study found significant differences in FVIII potency observed and indicated that it was likely to be due to the different rates of FX activation of individual kits.

In addition, in his second presentation, he described other collaborative studies, including a field study to investigate, "assay variability in potency assessment of recombinant FVIII products and a FVIII inhibitor using the South Mimms Inhibitor Assay," both of which highlighted discrepancy issues relating to use of FVIII deficient plasma.

Dr. Stella Williams (NIBSC, the United Kingdom) presented, "An introduction to the measurement of procoagulant activity in immunoglobulin products." Human plasma-derived immunoglobulin is considered to be a safe and effective treatment for a variety of autoimmune, infectious, transplantation-related, and chronic diseases. During 2010, an increase in thromboembolic events was observed after the administration to patients of certain Octagam 5% intravenous immunoglobulin (IVIG) lots. The cause was identified as an increase in activated factor XI in the final product. In 2012 the production section of the Ph. Eur. monograph for normal human immunoglobulin for intravenous administration was revised to state that, "The method of preparation also includes a step or steps that have been shown to remove thrombosis-generating agents" [4]. However, no officially approved methods for detecting thrombosis generating agents in immunoglobulins exist.

She described a number of assay methods that could be used including the thrombin generation assay (TGA) which is increasingly being explored as a global assay for detecting thrombogenic agents in immunoglobulin products. Typically, the test is performed by mixing test solution with plasma (pooled normal or FXI-deficient) and adding phospholipids, tissue factor, and a fluorogenic peptide substrate for thrombin. Thrombin formation is then initiated by the addition of calcium. The activated factor XI in the IVIG triggers the initiation of the intrinsic coagulation pathways, leading to thrombin generation [5].

Another method under consideration which is a universal assay used to detect activated coagulation factors in therapeutics and especially FIX concentrates and prothrombin complex concentrates called NaPTT. The assay is performed by adding the test sample to plasma, phospholipids and calcium; the presence of activated clotting factors is indicated by a shortening of the clotting time [6].

The final method is the FXIa functional chromogenic assay which is based on a purified system and is specific for the detection of FXIa (not a global assay). Currently, there are 2 commercial kits available which work on a similar principle; FXIa in the test sample is able to activate FIX into FIXa which in turn activates FX into FXa. The amount of FXa is determined from the hydrolysis of a chromogenic FXa substrate and is proportional to the FXIa activity in the sample. The International Reference Reagent, established in 2012 and the 1st International Standard for factor XIa, established in 2013, have been helpful in the development and refinement of assay methods to detect FXIa in immunoglobulins. However, no agreed limits or specifications exist for these tests.

In 2014, a global working group for the measurement of procoagulant activity of immunoglobulins was formed to develop harmonized methods and appropriate reference materials. The first immunoglobulin stakeholder forum, held in Rockville, USA on 7-8 September 2016, agreed that despite the availability of commercial assay kits and an international standard for factor XIa, high variation persisted in laboratory performance of these methods, which could lead

to discrepancies in the results. Therefore, small collaborative studies are currently being launched to further develop these assay methods.

Dr. Kiyoko Nojima (NIID, Japan) explained the standardization of the anti-complement activity of intravenous immunoglobulin (IVIG) in Japan. She reported that when IVIGs are administered to humans, immunoglobulin aggregates may nonspecifically activate the serum complement, causing severe adverse events including anaphylaxis [7, 8]. To reduce these risks and prevent such events, anti-complement activity (ACA) testing is required before marketing. Therefore, this test is performed as one of the blood safety tests for IVIGs according to the Minimum Requirements for Biological Products under the Japanese Pharmaceuticals and Medical Devices Act [9]. Furthermore, she stated that a collaborative study between NCLs and Japanese manufacturers was performed to standardize the ACA testing methods for globulin products. The results showed a large inter-laboratory difference between ACA values, so NIID established reference materials to normalize the ACA values relative to the assigned ACA value. As a result, the inter-laboratory difference was reduced, validating the reference material as it dramatically reduced the differences in the ACA values between the manufacturer and the NCL. She also mentioned the possibility of a collaborative study in the WPR.

Dr. Hokyung Oh (NIFDS, the Republic of Korea) presented a study on the standardization and establishment of the testing method for thrombin generation in Korea. In June 2013, the MFDS instructed the manufacturers of immunoglobulin products to add information describing the risk of thrombosis and strategies for mitigating the risk mentioned in the label, although no thromboembolic events associated with the use of domestically manufactured immunoglobulin products have yet been reported in Korea. Moreover, in several collaborative studies, NIFDS confirmed that the manufacturing processes of all types of domestic immunoglobulin products effectively eliminated procoagulant activities. Specifically, 99 lots of IVIGs (< 2 mIU/mL FXIa) and 13 lots of intramuscular immunoglobulins (3.0 ~ 7.9 mIU/mL FXIa) manufactured from April 2015 to September 2017 showed no significant procoagulant potential.

Prof. Dong-Yeop Shin (Seoul National University Hospital, Republic of Korea) presented an overview of IVIG-associated thrombosis from the clinician's perspective. He briefly introduced the common usage and adverse events of IVIG in clinic to provide the participants with a practical understanding and then presented an overview of the epidemiology, mechanism, clinical presentation, risk factors and clinical considerations of IVIG-associated thrombosis. The development of arterial or venous thrombosis after IVIG infusion is initially caused by residual coagulation factors and their zymogens in the IVIG preparation (e.g., factor XIa). However, many underlying patient risk factors also contribute to the thrombogenic potential. Arterial thrombosis usually occurs within 24 hours after IVIG infusion, while venous thrombosis can be delayed by more than 7 days from IVIG treatment. Despite the high mortality rate of IVIG-associated thrombosis, the exact incidence of IVIG-induced thrombosis has not yet been well established due to the limited data and many confounding factors. A recent Korean multi-institutional single-arm Phase III study examining the efficacy of 10% IVIG, enrolled a total of 81 patients and reported that no patients experienced thrombosis. An ethnic difference might exist in IVIG-associated thrombotic risk, and again, the incidence of IVIG-associated thrombosis is too low to detect in a prospective clinical trial. Clinician's careful attention is critical for the timely detection and appropriate management of IVIG-associated thrombosis because of its rarity.

Dr. Kiyoung Yoo (Korean Hemophilia Foundation, Republic of Korea) presented a clinical study on the global hemostatic assay to assess the objective hemostatic efficacy of factor VIII and factor IX concentrates in Korean hemophilia patients. The study compared the hemostatic efficacy of factor VIII and factor IX at different target activities with global hemostatic assays including TGA. According to the Korean health insurance guidelines, the target activities of factor VIII and factor IX are 60 IU/dL and 40 IU/dL. The study enrolled 34 patients with severe hemophilia A, 36 patients with hemophilia B, and 34 males without hemophilia as the control group. After infusions of the calculated dosage of each drug, TGA was performed. The post-infusion peak thrombin concentration in patients with hemophilia A and B were 116.6 nM/L and 76.4 nM/L ($p < 0.001$), respectively. The post-infusion endogenous thrombin potential (ETP) values in patients with hemophilia A and B were 1349.8 nM min and 915.6 nM min ($p < 0.001$), respectively. This study concluded that the currently reimbursed dosing for FIX concentrates is insufficient to deliver a hemostatic response comparable to that expected from the reimbursed dosing for FVIII concentrates in terms of peak thrombin concentration, ETP.

Discussion

Update on global activities

The third meeting of the network of the WHO vaccine standardization collaborating centers held in Osong, Korea on 30 June 2 July 2016 agreed to establish a Core Expert Group to advise the WHO on biological standardization program. The fourth meeting will be hosted by the NIFDC in 2018. In addition, it was announced that the first general meeting of NCLs, predominantly NCLs that have experienced a control test of the WHO prequalified vaccines, would be hosted by India on 30 Oct–2 Nov 2017. Four NCLs from the Western Pacific Region

namely, Australia TGA, China NIFDC, Japan NIID, Korea NIFDS have expressed interest in participating in this network. The main objectives of the WHO PQ-related NCL network are 1) to share quality and technical information related to prequalified products (vaccines or other biological medicinal products), 2) to facilitate recognition of the responsible NRA/NCL lot release by recipient countries, and 3) to promote the development of harmonized standards and best practices. Recently the representatives of China, Japan, Korea and Vietnam NCLs participated in the seventh meeting of SEAR NCLs held in December 2016 to share information and discuss matters of common interest.

Update on regional activities

The WHO WPRO plays a secretariat role for the regional alliance of NRAs. By adopting NRA benchmarking as a core strategy in coordination with the alliance's steering committee, the WHO WPRO has successfully helped all participating NRAs from middle income countries in particular to undergo self-assessment and development of institutional plans. In light of the WHO support for the strengthening of regulatory systems and the advancement of collaboration regarding global regulatory science agendas, the WHO WPRO has actively been engaged in a China-Japan-Korea tripartite biennial event entitled, "Symposium on Research and Quality Control of Vaccines." The third event was convened by NIFDC at its new campus in Beijing in May 2017. Key topics included a review of the vaccine Lot Release Systems in China, Japan and Korea, research on evaluation methods for vaccines, novel research on vaccines and the consideration of guidelines for the production and control of an enterovirus (EV)-71 vaccine to prevent hand, foot and mouth disease (HFMD).

Progress and key findings of WPR NCL agenda

Regarding the progress of a collaborative study on anti-venom references using LD50 and MHD assays, a proposal was raised by NIFDS and supported by the participating NCLs, at the first NCL meeting in 2016 [10]. Regarding the plans for a collaborative study on Factor XIa in plasma-derived products, NIFDS described a feasibility study on the selection of study materials and test methods. In the collaborative study proposal session, establishment for the first national reference standard of *Glodius* antivenom and alternatives to in vivo PRNT were proposed by NIFDS, and testing for freedom from aggregated immunoglobulin was suggested by NIID. A quick survey was designed and conducted to map whether countries are implementing the risk-based official lot release of vaccines and plasma-derived products. China, Japan and Korea implement a review of the summary lot protocol (SLP) or both SLP review and testing for vaccines. China reported that the frequency of testing is varied based on the risks assigned to a specific vaccine product, while Japan performs testing for all lots and a risk-based approach is currently under development. Malaysia conducts SLP review and cold chain inspection at the warehouse upon arrival at the port. The Philippines conducts SLP review only. Regarding plasma-derived products, Japan tests all lots, but implementation of SLP review and a risk-based approach is currently under discussion. Korea plans to make an improvement in risk-based approach for lot release for vaccines and blood products.

Risk-based approaches were further elaborated and tabulated under indicator, sub-indicator and risk categories. The listed indicators included the nature of the product, indications, history of production, history of GMP inspection, history of NCL testing, occurrence of adverse events, use history and NCL competency. Consultation with a series of experts was deemed necessary to develop further detailed guidance. Throughout the 2-day meeting, the following points of communication with the WHO Headquarters counterpart were proposed: 1) a more systematic and broader information sharing with all concerned and 2) the WHO guidelines on the introduction of SLP review and risk-based lot release for plasma-derived products. Information sharing is well established via the publication of the adopted documents at the WHO website and the ECBS SharePoint site and the publication of the WHO technical report series and draft documents during the annual proceedings of the WHO ECBS, particularly the annual compendium of reference standard project proposals and draft reports of collaborative studies.

Way forward

The participants agreed in principle to report the progress on risk-based official lot release by consolidating country mapping and framework guidelines. The NIFDS proposed a plan for a collaborative study on in vitro potency testing of the cell-based JE vaccine: method validation in 2018, initiation of the collaborative study in 2019, and review of the results in 2020. NIFDS also proposed a collaborative study to establish the first national reference standard for *Gloydius* anti-venom. NIID proposed conducting a survey on the minimum requirements and test methods for an anti-complementary effect assay of immunoglobulin aggregation content in intravenous immunoglobulin products.

Conflicts of Interest

The authors have disclosed no potential conflicts of interest.

Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the participating NCLs in preference to others of a similar nature that are not mentioned.

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References

[1] Isbrucker R, Sontakke S, Smith D. Health Canada's human vaccine lot release program: impact on the 3 Rs. Procedia Vaccinol 2011;5(Supplement C):147-50.
[2] Takeshita N, Lim CK, Mizuno Y, et al. Immunogenicity of single-dose vero cell-derived Japanese encephalitis vaccine in Japanese adults. J Infect Chemother 2014;20(4):238-42.
[3] Kim BC, Kim DK, Kim HJ, et al. A collaborative study of an alternative *in vitro* potency assay for the Japanese encephalitis vaccine. Virus Res 2016 ;223:190-6.
[4] Human normal immunoglobulin for intravenous administration. Monograph, European Pharmacopoeia: 01/2012:0918
[5] Grundmann C, Kusch M, Keitel S, et al. Modified thrombin generation assay: application to the analysis of immunoglobulin concentrates. WebMedCentral Immunotherapy 2010 Nov;10:C001116.
[6] Germishuizen WA, Gyure DC, Stubbings D, et al. Quantifying the thrombogenic potential of human plasma-derived immunoglobulin products. Biologicals 2014;42(5):260-70.
[7] Ramasamy I, Tran E, Farrugia A. Measurement of anticomplementary activity in therapeutic intravenous immunoglobulin preparations. Biologicals 1997;25(1):87-92.
[8] Nojima K, Okuma K, Ochiai M, et al. Establishment of a reference material for standardization of the anti-complementary activity test in intravenous immunoglobulin products used in Japan: A collaborative study. Biologicals 2017 ;46:68-73.
[9] Ministry of Health, Labour and Welfare, Japanese government Minimum Requirements for Biological Products: Test for freedom from anti-complement activity. 2004. Available from: https://www.niid.go.jp/niid/ja/mrbp.html
[10] Oh H, Shin J, Ato M, et al. The first meeting of the national control laboratories for vaccines and biologicals in the Western Pacific in 2016. Osong Public Health Res Perspect 2017 ;8(1):91-103.