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International Alliance for Biological Standardization

IABS International Meeting

Maintaining the Quality of Vaccines Through the Use of References Standards: Current Challenges and Future Opportunities

June 21-22, 2023

Library and Archives Canada

Ottawa, Canada

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About the Conference

To discuss both technical and regulatory considerations specific to the use of reference standards in the quality control of human and veterinary vaccines.

Given the different approaches currently in practice, the aim is to agree with a set of principles that can be used to ensure consistency of vaccine products against the specifications approved in their Marketing Authorization. A particular emphasis will be placed on the appropriate regulatory oversight and how should national regulatory authorities and international standard-setting bodies coordinate their activities to ensure the consistency of vaccine products against the specifications approved in their Marketing Authorization.

This meeting will bring together regulators, scientists, and industry experts to help resolve existing challenges and to reach consensus that will be valuable in adopting a common approach.

Scientific and Organizing Committee

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Maria BACA-ESTRADA Co-Chair; Health Canada, Canada

Carmen JUNGBÄCK Co-Chair; International Alliance for Biological Standardization (IABS), Germany

Ryan BRADY Merck Animal Health, U.S.A.

Alexander ZAKHARTCHOUK Canadian Food Inspection Agency

Rick HILL President, International Alliance for Biological Standardization (IABS), U.S.A.

Richard ISBRUCKER World Health Organization (WHO), Switzerland

Laurent MALLET European Directorate for the Quality of Medicines & HealthCare (EDQM), France

Catherine MILNE European Directorate for the Quality of Medicines & HealthCare (EDQM), France

Pieter NEELS International Alliance for Biological Standardization (IABS), Belgium

Tim SCHOFIELD CMC Sciences, LLC, U.S.A.

Dean SMITH; Health Canada

Paul STICKINGS Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom

Catrina STIRLING Zoetis, United Kingdom

Sylvie UHLRICH Sanofi, France

Ester WERNER Paul-Ehrlich-Institut (PEI), Germany

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08:00 – 08:40 Registration & Welcome Coffee

08:30 – 09:00 Opening of the meeting - **Shawn NOVICK on behalf of Rick HILL, President, International Alliance for Biological Standardization**

Session 1: Use of Reference Standards and Regulatory Expectations

The focus of this session is to introduce the different uses of reference standards, performance standards and controls with the aim of proposing the use of the same terminology throughout this meeting. In addition, the presentations will provide different perspectives and will highlight some of the challenges in the implementation and use of Standards.

Chairpersons: Sylvie UHLRICH, Sanofi, France
Tim SCHOFIELD, CMC Sciences, LLC, U.S.A.

09:00 – 09:30 An overview of the contribution of reference standards to the quality control of vaccines - **Catherine MILNE, European Directorate for the Quality of Medicines & HealthCare (EDQM), France**

09:30 – 10:00 Development and Implementation of WHO measurement Standards for vaccines - **Tiequn ZHOU and Dianliang LEI, Norms and Standards for Biologicals, World Health Organization**

10:00 – 10:30 Case study: Human vaccine in vitro relative potency reference standard qualification in ELISA - **Geoffrey DUBY; Marie-Claire BECKERS; Delphine VANHAM, GSK Vaccines, Belgium**

10:30 – 11:00 Break

11:00 – 11:30 Regulatory expectations on the use of vaccine reference standards for maintaining product quality - **Wim VAN MOLLE; Sciensano, Belgium**

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11:30 – 12:00	Challenges when assessing multi component vaccine formulations **Paul STICKINGS, Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom**
12:00 – 12:30	WOAH Procedure for Development, Validation and Adoption of Standards for Veterinary Vaccines and Reagents - **Glen GIFFORD; Maria SZABO, World Organisation for Animal Health**
12:30 – 01:30	Lunck Break
01:30 – 02:00	Regulatory expectations - veterinary vaccines - **Angela WALKER/ Geetha B. SRINIVAS, U.S. Department of agriculture (USDA)**
02:00 – 02:30	Panel Discussion

Session 2: Principles and Practices: Technical and Regulatory Expectations

In this session, presenters will describe principles and practices as viewed from a "fitness for use" point of view. They will also highlight the regulatory expectations regarding the design and management of standards programs including the approaches to qualify/calibrate and monitor the stability of standards.

Chairpersons: Carmen JUNGBÄCK, IABS, Germany
Paul STICKINGS, Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom

02:30 – 03:00	Principles and practices for reference standards - **Tim SCHOFIELD, CMC Sciences, LLC, U.S.A.**
03:00 – 03:30	Current approaches in the establishment of International Reference Standards for vaccines - **Peter RIGSBY, Medicines and Healthcare products Regulatory Agency (MHRA) United Kingdom**
03:30 – 04:00	Break

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04:00 – 04:30	Scientific considerations for implementing and maintaining reference standards for the lifecycle management of vaccines - **Tong WU, Health Canada**
04:30 – 05:00	Regulatory perspectives on Reference Standard management protocols for vaccines - **Gayle PULLE, Health Canada**
05:00 – 05:30	Use of Reference Standards to monitor product quality: US FDA perspective - **Swati VERMA, Center for Biologics Evaluation and Research, US Food and Drug Administration**
05:30	End of Day 1

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Session 3: Principles and Practices: Industry Practices and Experiences

This session will cover manufacturers' approaches to the implementation and standards programs highlighting the challenges and the opportunities to monitor the quality of vaccines throughout the life-cycle. Case studies will be presented to provide insights into some of the current issues and opportunities for improvement.

Chairpersons: Laurent MALLET, European Directorate for the Quality of Medicines & HealthCare (EDQM), France
Dean SMITH, Health Canada

08:30 – 09:00	Qualification and stability monitoring of reference standards in the U.S. animal health industry and current challenges - **Ryan BRADY, Merck Animal Health, U.S.A.**
09:00 – 09:30	Standardization and implementation of existing international reference standards for high throughput multiplex immunoassays - **Manish GAUTAM, Sunil GAIROLA, Serum Institute of India**
09:30 – 10:00	Experience on the implementation and the use of reference standards for human vaccines potency testing - **Sylvie UHLRICH, Emmanuelle COPPENS, Sanofi, France**
10:00 – 10:30	Break
11:00 – 12:00	Panel Discussion **Speakers from Session 2 and 3**
12:00 – 01:00	Lunch Break

Breakout sessions:

The purpose of these sessions is to have small groups address the most "burning" issues discussed during the meeting. Groups will be divided into 3 topics: (1) standards programs and regulatory expectations, (2) qualification programs and (3) stability programs.

- 1-hour discussions based on prepared questions
- Facilitators organize discussion and take notes
- Facilitators will report to the whole group during the Workshop Summary and Conclusions.

Chairpersons: Laurent MALLET, European Directorate for the Quality of Medicines & HealthCare (EDQM), France
Dean SMITH, Health Canada

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01:00 – 02:00	Breakout groups convene
02:00 – 02:30	Break

Session 5: Perspectives from other fields in the use of reference materials

Chairpersons: Richard ISBRUCKER, Health Canada

02:30 – 03:00	The role of International Standards for Monoclonal Antibodies in supporting bioassay data harmonisation: perspectives from the human biotherapeutics field - **Sandra PRIOR, Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom**
03:00 – 03:30	The use of reference materials in the standardization of immunological assays **Valentina BERNASCONI, Coalition for Epidemic Preparedness Innovations (CEPI), United Kingdom**
03:30 – 04:00	The Future of Reference Standards for Vaccines - **Diane McCARTHY, United States Pharmacopeia (USP)**
04:00 – 05:00	Summary and Conclusions of Breakout Session **Laurent MALLET, European Directorate for the Quality of Medicines & HealthCare (EDQM), France** **Dean SMITH, Health Canada**
04:00 – 05:00	**Meeting Conclusions and Recommendations :** • Have we achieved the objectives of the meeting? • Do we have consensus on a set of principles and best practices in the development and implementation of standards? • What are the gaps and next steps?
05:00	Closing remarks - **Carmen JUNGBÄCK, IABS**
05:00	End of Meeting

Upcoming IABS Conferences and Workshops

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2023

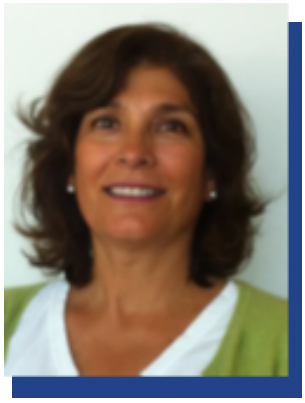
IABS – Flanders Vaccine The Role of Real-World Evidence for Regulatory and Public Health Decision Making for Accelerated Vaccine Deployment

Leuven, Belgium
September 19-20, 2023

9th Annual Statistics Workshop Statistical Innovation Advancing CMC

Rockville, USA
November 7-9, 2023

Biosketch



Maria Baca-Estrada

Manager, Clinical Evaluation Vaccines Division.
100 Eglantine Driveway, Ottawa, ON K1A0K9,
Canada.
Health Canada

E-mail: maria.baca-estrada@hc-sc.gc.ca

Dr. Maria Baca-Estrada received her PhD in immunology from the University of Glasgow, UK. She worked at McMaster University (Canada) as a post-doctoral fellow and later as a Research Scientist at the Vaccine and Infectious Disease Organization (Canada).

Her research included approaches to develop new vaccine formulations and alternative routes of vaccine administration. She joined Health Canada in 2002 as a regulatory Scientific Evaluator and was later appointed Manager of the Bacterial and Combination Vaccines Division. Dr. Baca-Estrada left Health Canada for 2 years to work at the World Health Organization as a Scientist with the Quality, Safety and Standards team and participated in the development of WHO guidelines and recommendations to support regulatory evaluation of vaccines.

Dr. Baca-Estrada returned to her position in Health Canada and continues to be actively involved in international collaborations with many organizations in this area. She has been recently appointed Manager of the COVID-19 Clinical Evaluation Vaccines Division.

Biosketch

Marie-Claire Beckers

Global Subject Matter Expert for QC materials management and Sampling & Sample management
1300 Wavre Belgium
Vaccines Global Quality Control and Product Quality at GSK

Tel: +32 497147514
E-mail: Marie-Claire.x.Beckers@gsk.com

Marie-Claire Beckers received her doctoral degree from the University of Liège (Belgium)at the laboratory of Genetics of the Microorganisms. She did a post-doctoral fellow at the Biochemistry Department of McGill University (Montreal, Canada), in the field of molecular genetics. She worked at Eurogentec, a biotechnology company for 12 years as Team Leader of DNA sequencing and as New Product Development Manager in the Life Sciences.

She is co-inventor of four patents. Before to join GSK, she was Preclinical manager and Head of production in biopharmaceutical companies. Since 2017, she is Senior Manager, Global Subject Matter Expert for Sampling and Sample Management and for QC materials Management at GSK.

Abstract

Marie-Claire Beckers, Geoffrey Duby & Delphine Vanham

Case study: Human vaccine in vitro relative potency reference standard qualification in ELISA

Background

GSK is a global biopharma company with a purpose to unite science, technology, and talent to get ahead of disease together and is a major actor in the human vaccine supply world.

Challenges

Qualification of in-house biological reference standards used in in vitro relative potency ELISA test for release of new human vaccine material is complex to manage:
• No international reference standards are yet available.
• The limited initial reference standard stock leads to the need of managing multiple changes prior to identifying the primary/gold reference standard.
• The stability data package of the initial representative material is often limited (less than 5 years) at the time of regulatory submission.
• Changes of reference material during method lifecycle require an agreement from multiple different authorities which leads to a complex implementation strategy.
• Challenge for transferring Quality Control materials to National Control Laboratories or to other sites with relevant and complex importation requirements.

Proposed approach being taken

We propose to share a practical case-study of in-house biological reference standard qualifications and managements.
• Two approaches will be presented to define how an antigen content value can be determined: using either an absolute orthogonal method or using an antigen specific content method. In addition to the antigen content, the potency value of the primary/gold reference standard, representative of Phase III and supporting the efficacy of the vaccine, is assigned to 100%.

Abstract

• To support the change of working reference standard lot, instead of using a two-tiered approach to bridge each reference standard to the primary reference standard, we propose the use of a one-tiered approach considering the successive comparability of the new reference standard versus the current one. Based on the product and process knowledge, the difference between new and in-use reference standards is expected to fall within a pre-defined interval depending on the method performance and therefore a 100% potency will be assigned to the new reference standard. This approach circumvents the impact of some potential stability evolutions and error propagation inherent to the application of corrective factor.
• Finally, to facilitate the lifecycle management and anticipate the change of reference standards, pre-approved qualification protocols are shared with authorities allowing to smooth and accelerate the new reference standard implementation.
• With a continued growth of vaccines in the coming years, we propose to improve the robustness of the transfer process to cope on the specific demands of National agencies and the importation process.

Biosketch

Valentina Bernasconi

Head of Laboratory Science
Oslo, Norway
CEPI

Tel: +47 94002534
E-mail: ryan.brady2@merck.com

Valentina Bernasconi, Ph.D., is an immunologist with 8 years' experience in planning, managing, and executing projects spanning early and late preclinical discovery for infectious diseases vaccination in both industry and academy settings. Currently Head of the Laboratory Science group at the Coalition for Epidemic Preparedness Innovation (CEPI), she is leading the CEPI Centralized Laboratory Network for immunogenicity testing vaccine candidates, which includes 15 laboratories worldwide. She holds a master's degree in Medical and Pharmaceutical Biotechnology form Vita-Salute San Raffaele University, Milan, Italy and a PhD in immunology from University of Gothenburg, Gothenburg, Sweden. She has earned a master's degree in Global Health Policy from the London School of Hygiene and Tropical Medicine, London, UK.

Abstract

Valentina Bernasconi

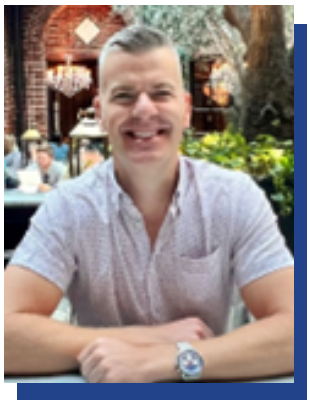
The use of reference materials in the standardization of immunological assays

Comparing immune responses against different vaccine candidates intended for the prevention of a specific viral infection is challenging. To improve immunological assay standardization across different vaccine candidates and meaningful comparison of results, the Coalition for Epidemic Preparedness Innovations (CEPI) has created a Centralized Laboratory Network (CLN) vaccine immunogenicity testing selecting laboratories with high quality standards worldwide, picking the most advanced assays to be used across the Network and providing all the laboratories with harmonized of protocols and key reagents. The Network has worked on SARS-CoV-2 assay since it's creation in 2020 and is now expanding to new pathogens.

The Centralized Laboratory Network today counts 15 laboratories worldwide, is open to all vaccine developers worldwide to apply for testing samples from pre-clinical to Phase III clinical studies to facilitate rapid evaluation, approval, and dissemination of the most effective vaccine candidates and supports their pathway towards licensure.

The CLN focuses on immunological assays including antibody binding assays, neutralizations assay, and an immune cell-based assay. The assays are developed, qualified and validated in one reference laboratory and then transferred to the rest of laboratory partners for suitable use in clinical trials in accordance with the regulatory guidelines. All CLNs use the same key reagents, comparable materials and equipment, parallel protocols and procedures, and well characterized standards and panels including the WHO international antibody standards to ensure accuracy, reproducibility and harmonization of assay results. The use of standards material is useful in assay harmonization efforts but also has its challenges.

Biosketch



Ryan Brady

Associate Director, Quality & Compliance
Kansas City, MO, USA
Merck Animal Health
35500 W. 91st St., De Soto, KS 66018, USA

Tel: +1 913 422 6049
E-mail: ryan.brady2@merck.com

In his current role with Merck Animal Health, Ryan oversees the management of reference standards for multiple U.S. sites, which are used for relative potency estimation of licensed biological products. His responsibilities include leading the qualification of new reference standards, developing and implementing stability monitoring programs for reference standards, and ensuring compliance with USDA regulations. Ryan has over 18 years of experience in the U.S. animal health biologics industry, including 7 years in Biological Research and Development, and was involved in the licensure of several flagship products for Merck Animal Health.

In addition to managing the reference standard program for Merck Animal Health, Ryan serves as a study director and technical support lead for numerous analytical projects, including the development and validation of in vitro potency and stability monitoring assays, transfer of test methods between departments and sites, as well as assay troubleshooting and optimization activities in support of licensed biological products.

Ryan obtained both a B.S. and M.S. in Veterinary and Biomedical Sciences from the University of Nebraska, Lincoln. His graduate research involved the creation and evaluation of DNA constructs encoding the attachment glycoprotein of bovine respiratory syncytial virus.

Abstract

Ryan Brady

Organization: Merck Animal Health

Qualification and stability monitoring of reference standards in the U.S. animal health industry and current challenges

Introduction: The USDA has specific guidance outlining expectations for the qualification and stability monitoring of reference standards used in potency testing of veterinary vaccines. The reference standard used in a relative potency assay is correlated, directly or indirectly, to host animal immunogenicity. The stability monitoring requirements for reference standards are dependent on the product licensure status as of January 1, 2011. Reference standards may be allowed up to 15 years, or continuous dating, based on the approved reference monitoring plan.

Challenges: Merck Animal Health has approximately 30 reference standards reaching their 15-year expiration within 5 years, which will require qualification of new reference standards. This phenomenon is impacting the entirety of the U.S. animal health industry. According to USDA regulations, the qualification study must use the same animal model and efficacy study design that supported initial licensure or the most recent reference qualification. The industry expects to encounter numerous challenges with these in vivo qualification studies including the identification of seronegative animals, confirming viability of existing challenge strains, and replicating intricate animal study designs.

Current Approach: To maintain 15-year dating, serial release testing data is trended and reference monitoring reports are supplied to USDA at 2.5-year intervals. For reference standards of newly licensed products, licensed in 2011 or later, a freeze-thaw degradation study must be successfully performed to attain 15-year dating. In addition, firms can elect to develop one qualitative and one quantitative test to monitor the reference, which could support indefinite dating for the newly licensed product reference. The ability to detect and correlate degradation across assays is a key component during validation; however, reference standards are often product-matched, containing multiple antigen components as well as adjuvant which makes such method development challenging.

Conclusions: Qualification of reference standards and the development of reference stability monitoring assays are lengthy and resource-intensive processes for the U.S. animal health industry.

Biosketch

Emmanuelle Coppens

Global Analytical Expert, Analytical Sciences
69280 Marcy l'Etoile, France
Sanofi Vaccines

Tel: +33 (0) 6 71 14 63 30
E-mail: Emmanuelle.coppens@sanofi.com

Dr Emmanuelle Coppens is a Global Analytical Expert in 3Rs and Immunology with the mission to coordinate removal of in vivo analytical testing within Sanofi vaccines company. She graduated from French National Veterinary school with a specialty diploma in laboratory animal science and with a thesis in Molecular Virology. After a first experience in Pierre Fabre (human medicine company) research center Animal Resources department (Castres, France), she joined Sanofi Pasteur (Human vaccines and sera company) Quality Control (QC) department in the vicinity of Lyon, France.

She was head of a QC laboratory unit dedicated to analytical testing and animal derived reagents production and then moved to transversal activities. In parallel to being expert in neurovirulence and tumorigenicity (histopathology), she was in charge of analytical lifecycle management projects as well as compendial monitoring for in vivo analytical testing and AAALAC accreditation of animal facilities.

Her fields of expertise are in vivo & in vitro bioassays, neurovirulence and safety in vivo testing, applicable to human vaccines and biologicals. She is a member of EPAA Industrial Steering Committee and of EPAA project "3Rs Harmonization in Biologicals" as well as a member of expert working group within NC3Rs project "Review of animal use requirements in WHO biologics guidelines".

Abstract

Emmanuelle Coppens & Sylvie Uhlrich

Experience on the implementation and the use of reference standards for human vaccines potency testing

Sanofi Vaccines, Marcy l'Etoile, France

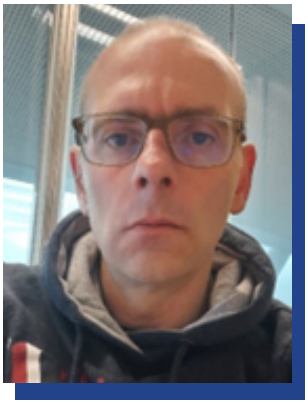
As an introduction, general practices at Sanofi Vaccines for the choice and qualification of reference standards will be described as well as their stability monitoring. A focus will be made on qualification study design in the frame of the replacement of a reference standard.

Two case studies on Tetanus in vivo potency and Polio D antigen assays, where a change to a new IRS (International Reference Standard) showed an impact on product consistency with risk of out of specification results, will be shared. For each case, a similar root cause was identified related to the methodology for assigning the titer of the IRS. A common remediation plan based on the implementation of an in-house reference will be presented.

General recommendations on the establishment of IRS will be made. The respective use of an IRS or in-house reference standard will be discussed.

This work was funded by Sanofi.
Emmanuelle Coppens and Sylvie Uhlrich are Sanofi employees and may hold shares and/or stock options in the company.

Biosketch



Geoffrey Duby

Senior Manager, Strategy and Validation of Critical Test Reagent
1300 Wavre, Belgium
Quality Control at GSK

Tel: +32 478734191
E-mail: Geoffrey.x.duby@gsk.com

Geoffrey Duby is a Chemical and biotechnical engineer and hold a PhD in biochemistry from the University of Louvain-la-Neuve, Belgium. He has been leading research teams in the university for 7 years on projects related to biochemistry before joining the industry. He started in 2011 as pilot plant team leader in a vaccine company and was principal scientist on formulation. He acquired experienced in product transfer and in vaccine development.

In 2017 he joined GSK in the Analytical Strategy and Technology Innovation department. He is leading the strategy and validation of critical test reagents within the QC at GSK Wavre site. He has led the continuous method validation and he is a subject matter expert in QC on the reagent management and qualification.

Abstract

Marie-Claire Beckers, Geoffrey Duby & Delphine Vanham

Case study: Human vaccine in vitro relative potency reference standard qualification in ELISA

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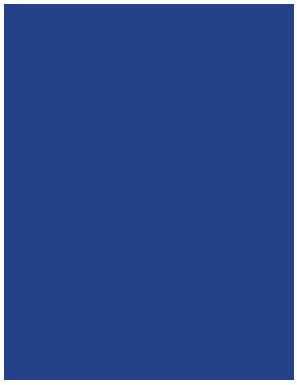

Dr. Sunil Gairola, M. Phil, Ph. D.

Executive Director
Serum Institute of India Pvt. Ltd.,
212/2, Hadapsar, Pune - 411 028, India

Tel: + 91 20 2660 2395
Fax: +91 20 26993945
E-mail: sunil.gairola@seruminstitute.com
sgairola.gairola2@gmail.com

Sunil Gairola is the Exécutive Director at Serum Institute of India Pvt. Ltd.
More than 40 years of experience in several functions of quality control, quality assurance and clinical bioanalytics of vaccines and biosimilars. Part of product devlopment leadership teams for newer vaccines and registration of vaccines in developed and emerging markets. Leads more than 500 scientists working on analytical development and characterization of bacterial, viral, recombinant, sub-unit and viral vector-based vaccines. Collaborator to international initiatives of WHO, NIBSC, EDQM, and PATH, aimed at the harmonization of regulatory requirements, establishment and development of international standards. Member to scientific body of Indian Pharmacopeia and USP expert panels on vaccines and biosimilars. He also served for many years at National Control Laboratory, India. Also forged collaborative projects with West and Indian academia focussed on novel adjuvants, genomic surveillance of infectious diseases and use of newer technologies for vaccine testing and characterization. Authored more than 50 publications and has patents on vaccine development and analytics.

Abstract

Manish Gautam, Sunil Gairola, Kevin Markey & Laura Hassall

Standardization and implementation of existing international reference standards for high throughput multiplex immunoassays

Serum Institute of India Pvt Ltd, Pune, Maharashtra, India 411028.

Scientific Research & Innovation, Medicines and Healthcare products Regulatory Agency Blanche Lane, South Mimms, EN6 3QG, United Kingdom

Background: Multiplex immunoassays (MIA) such as Luminex x-MAP® and Meso Scale Diagnostics (MSD) offer opportunities for simultaneous quantification of multiple antigens in a single well. Several studies have reported the use of multiplex assays for immunogenicity testing of vaccines. It is important that such multiplex assays are developed and validated by reporting the results in units that are traceable to an appropriate international reference standard. There are challenges as currently available international standards are more suited to monoplex/conventional assays. The development of in-house reference standards for MIA has its own challenges as it requires serum samples with high antibody titers against all target antigens. Approaches based on the utilization of serum pools of vaccinated people may not be practical for all laboratories. This study reports on the implementation of existing international reference standards for use in a multiplex assay for quantification of antibodies against tetanus (T), Diphtheria (DT), Pertussis Toxin (PT), Filamentous hemagglutinogen (FHA) and Pertactin (PRN).

Material and Methods: Characterization of the existing reference standards to evaluate their suitability use for MIA assays are urgently required to develop MIA assays which are traceable to international reference standard. NIBSC/WHO provides three reference standards, namely TE-3, 10/262 and 06/142 which respectively have the unitages for T, D, and acellular pertussis (PT, FHA and PRN) antigens.

Results: The study proposes the unitages to all the five antigens for antibodies against PT, FHA, PRN, DT and TT in the TE-3, 10/262 and 06/142 which can be used to develop suitable reference standard for MIA assays. Using the NIBSC standards, the study describes a case study for development and validation of a 5-plex magnetic bead-based Luminex-based assay to quantify human IgG antibodies to DT, TT, and pertussis antigens.

Abstract

Conclusions: These unitages will provide opportunities for the use of these reference standards in multiplex assays. Development and validation of an assay against the international reference standard provides opportunities to harmonize and pool clinical results across multiple studies with good confidence and reproducibility.

Biosketch

Manish Gautam

Deputy General Manager
411028, Pune, Maharashatra, India
Serum Institute of India Pvt Ltd.

Tel: +91-20-26602858
E-mail: m.gautam@seruminstitute.com

Manish Gautam is a PhD in Pharmaceutical Sciences, currently working as team lead as General Manager at Serum Institute of India Pvt Ltd. He completed his PhD degree from University of Pune, India. He has extensive experience in several functions of analytical development, quality control and clinical bioanalytics of vaccines. Team lead on clinical bioanalytics with focus on clinical immunogenicity of vaccines. Leading an analytical group focused on development of analytical methods and quality control of Pneumococcal conjugate, acellular pertussis and Covid vaccines. He is also inventor to many patents on development of technologies concerning to Pneumococcal conjugate, acellular pertussis and novel adjuvants.

Reviewer to number of national and international medical journals. Before joining Serum Institute, he was a senior research associate to Govt of India drug discovery and development of immunomodulators and taught graduate and post graduate students at University department of Health Sciences. His areas of interest are immunology, vaccine analytics and vaccine adjuvants. He is the member of Indian Pharmaceutical Association.

Abstract

Manish Gautam, Sunil Gairola, Kevin Markey & Laura Hassall

Standardization and implementation of existing international reference standards for high throughput multiplex immunoassays

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Scientific Research & Innovation, Medicines and Healthcare products Regulatory Agency Blanche Lane, South Mimms, EN6 3QG, United Kingdom

Background: Multiplex immunoassays (MIA) such as Luminex x-MAP® and Meso Scale Diagnostics (MSD) offer opportunities for simultaneous quantification of multiple antigens in a single well. Several studies have reported the use of multiplex assays for immunogenicity testing of vaccines. It is important that such multiplex assays are developed and validated by reporting the results in units that are traceable to an appropriate international reference standard. There are challenges as currently available international standards are more suited to monoplex/conventional assays. The development of in-house reference standards for MIA has its own challenges as it requires serum samples with high antibody titers against all target antigens. Approaches based on the utilization of serum pools of vaccinated people may not be practical for all laboratories. This study reports on the implementation of existing international reference standards for use in a multiplex assay for quantification of antibodies against tetanus (T), Diphtheria (DT), Pertussis Toxin (PT), Filamentous hemagglutinogen (FHA) and Pertactin (PRN).

Material and Methods: Characterization of the existing reference standards to evaluate their suitability use for MIA assays are urgently required to develop MIA assays which are traceable to international reference standard. NIBSC/WHO provides three reference standards, namely TE-3, 10/262 and 06/142 which respectively have the unitages for T, D, and acellular pertussis (PT, FHA and PRN) antigens.

Results: The study proposes the unitages to all the five antigens for antibodies against PT, FHA, PRN, DT and TT in the TE-3, 10/262 and 06/142 which can be used to develop suitable reference standard for MIA assays. Using the NIBSC standards, the study describes a case study for development and validation of a 5-plex magnetic bead-based Luminex-based assay to quantify human IgG antibodies to DT, TT, and pertussis antigens.

Abstract

Conclusions: These unitages will provide opportunities for the use of these reference standards in multiplex assays. Development and validation of an assay against the international reference standard provides opportunities to harmonize and pool clinical results across multiple studies with good confidence and reproducibility.

Biosketch

Glen Gifford

Consultant
Ottawa, Canada

Tel: +1 613 229 0770
E-mail: glengifford.email@gmail.com

The World Organisation for Animal Health (founded as OIE) is an intergovernmental standard-setting organisation that develops and implements animal health technical standards and capacity building programs, through a global network of Members and collaborating experts. Dr Gifford completed his veterinary studies in Saskatoon, Canada at the Western College of Veterinary Medicine and the Vaccine and Infectious Disease Organization (VIDO). Throughout most of his career, he worked as a veterinary biologics evaluator and National Manager at the Canadian Centre for Veterinary Biologics, Canadian Food Inspection Agency in Ottawa, Canada. From 2016-2020 he was seconded to the WOAH headquarters in Paris.

During his secondment at the WOAH and subsequent consulting assignments, Dr Gifford's main responsibilities involved contributing to the development and revision of the WOAH's technical standards for vaccines, diagnostic tests, and reagents, which are published in the WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual).

Abstract

Glen Gifford & Mária Szabó

WOAH* Procedures for Development, Validation and Adoption of Standards for Veterinary Vaccines and Reagents
*Founded as OIE

Background: The World Organisation for Animal Health (WOAH, founded as OIE) is an intergovernmental standard-setting organisation that develops and implements animal health technical standards, including standards for vaccines and diagnostic tests, and capacity building programs, through a global network of Members and experts in Reference Laboratories and Collaborating Centres. WOAH standards are developed, validated, and adopted by Members in a science-based, transparent, democratic procedure. Once adopted, the standards are published in WOAH Codes and Manuals, which are applicable for all WOAH Members and become the internationally agreed basis for trade, under the World Trade Organization Sanitary & Phytosanitary (WTO SPS) Agreement.

Challenges: WOAH and the Food and Agriculture Organisation of the United Nations are jointly engaged in a comprehensive vaccination and testing program to control and globally eradicate a disease of sheep and goats, peste des petits ruminants (PPR), by 2030. The participating vaccine manufacturers, animal health workers and farmers in PPR infected regions of Africa, Middle East, Asia and Europe require timely access to safe and effective vaccines that conform to international quality standards, as published in the WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual). The PPR Global Eradication Program (PPR GEP) will require large scale production of conventional modified live PPR vaccines, as well as specialized vaccines, diagnostic tests, and reagents, such as: (1) vaccines with well characterized or enhanced thermotolerance properties for use in regions where the cold chain may be interrupted; (2) 'DIVA' vaccines and corresponding diagnostic tests for differentiating infected animals from vaccinated animals; and (3) clearly defined quality assurance standards for PPR vaccines to help ensure that manufacture consistently provide high quality vaccines while also conforming to the 3R principles for refining, reducing and replacing use of animals for laboratory testing and (4) PPR diagnostic tests and reference reagents for use in vaccine production and quality control.

Conclusions: To address animal health stakeholders' ongoing needs, including those of the PPR GEP, the WOAH continuously updates the relevant Terrestrial Manual standards for vaccines, diagnostic tests, and reagents. The slide presentation will review the key challenges and discuss some recent actions that have been undertaken to address them.

Biosketch

Rick Hill

President, IABS

Tel: + 1 515 435 2677
E-mail: arhill@iastate.edu

Dr. Richard E. Hill, Jr., (Rick) received a D.V.M. degree from Michigan State University in 1983 and following graduation, worked in private veterinary practice.

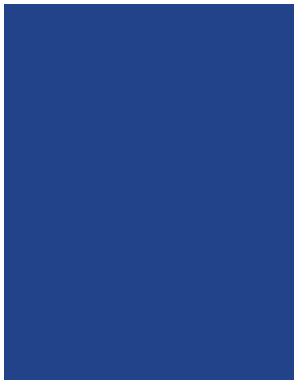
In 1985, he joined the USDA and worked as a field Veterinary Medical Officer before joining the Biologics Program in 1986. Rick worked as an Inspector, Epidemiologist, and Team Leader, for the Biologics Program where he was involved in regulatory compliance and coordination of the pharmacovigilance program.

In 1990, he received an M.S. degree in Veterinary Preventive Medicine at Iowa State University and is a Diplomate in the American College of Veterinary Preventive Medicine.
In 1995, Dr. Hill transferred to the position of Quality Assurance Manager, responsible for overseeing the Quality Assurance Program at the National Veterinary Services Laboratories and Center for Veterinary Biologics Laboratory.

In November 1998, he rejoined the Center for Veterinary Biologics as Director of Licensing and Policy Development and then served as the Center Director from 2005 through 2013.
In 2013, Dr. Hill assumed the position of Executive Director for Veterinary Services, National Import and Export Services until his retirement in 2016 after 30+ years of Federal service.

Biosketch

Richard Isbrucker



Biosketch

Carmen Jungbäck

IABS: Board Member, Secretary
IABS-EU Vice-Chair, Secretary
Germany

Dr Carmen Jungbäck graduated from the Tierärztliche Hochschule, Hannover with a degree in Veterinary Medicine. In 1981, after a few years as an animal surgeon she joined the Paul-Ehrlich-Institut, (Federal Agency for Sera and Vaccines), Langen, Germany, where she was Head of the section Veterinary Virology 1 until retirement in 2016. The section's area of activities comprises vaccine licensing and testing, with special expertise in viral vaccines for poultry. In this context, the practical testing of vaccines during licensing and for official batch release is one of the major responsibilities.

She was also member of a number of advisory boards to the EDQM-OMCL Network, Ph.Eur Group 15V and CVMP-IWP and JEG3R at EMA dealing with IVMPs under various aspects.

At IABS and IABS-EU she acts as Secretary. She is organizing IABS meetings focusing on the veterinary field. As member of IABS-EU she is involved in various EU--projects (ZAPI, Vac2Vac, MANCO).

Biosketch

Dianliang Lei, Ph.D.

Scientist
World Health Organization
Geneva, Switzerland

E-mail: leid@who.int

Dr Dianliang Lei received his doctor degree in medical science from Medical School of Osaka University Japan in 1996. He joined World Health Organization in 2003 as a scientist working in Technical Specifications and Standards unit of Health Product Policy and Standards department, responsible for development of WHO international standards including measurement standards and written standards for vaccines and biological products. He has been in charge of development of WHO Guidelines for lot release of vaccines, GMP for biological products, Guidelines for post-approval changes to vaccines, Guidelines for marketing authorization of pandemic vaccines in importing countries, Recommendations for acellular pertussis vaccines, DT-based combined vaccines, Hepatitis E vaccines, Enterovirus vaccines, yellow fever vaccines and Manual for calibration of secondary standards. Dr Lei, before joining WHO, was deputy director of National Institute for the Control of Pharmaceutical and Biological Products responsible for regulation, quality control and biological standardization of vaccines in China. He contributed to the strengthen the regulation system for vaccines in China, especially on the national requirements (pharmacopeia) for biologicals, standards, specification for vaccines and lot release system.

Abstract

Dianliang Lei & Tiequn Zhou

Development and Implementation of WHO measurement Standards for vaccines

Dianliang Lei, Tiequn Zhou, World Health Organization, Geneva, Switzerland

Developing international standards for biologicals and promote their implementation are core functions of the WHO. WHO establishes international measurement standards (IS) through the Expert Committee on Biological Standardization (ECBS), assigning unitage such as International Unit. These standards serve as the primary standard and are used by National Control Laboratories (NCLs) and manufacturers for the calibration of national and other secondary standards, including working standards, for quality control and evaluation of vaccines. They play a crucial role in ensuring the quality, safety and efficacy of vaccines worldwide.
Nowadays, many factors posed challenges to developing and implementing IS, including, but are not limited to:

• new and modern technologies: diverse types of vaccines for a single pathogen and broad range of assays in use may impact on the suitability and applicability of a unified IS.
• assignment of unitage to different types of assays: for example, assigning unitage for antibody-binding assays versus neutralization assays may be complicated.
• fast-evolving epidemiological situation in particular in a public health emergency, like the COVID-19 demands for rapid development of IS to respond to the rapidly changing situation.
• evolving development of vaccines: IS is usually needed and developed at early stage to facilitate vaccine development; however, vaccine development is dynamic and issues may arise when an IS is established after a product is licensed or before a new type of vaccine becomes available.
• need for proper understanding of IS and its use.

Timely development and provision of IS facilitate development, assessment and licensure of biological products, and enable comparability of data across different settings. After the establishment of standards, continuous technical support is crucial to ensure their appropriate use. Ongoing efforts are being made to provide technical support to Member States, targeting NCLs, vaccine developers and manufacturers, which include organizing implementation workshops to elaborate on and promote the use of WHO standards. Global collaboration and synergy among academia, kit and vaccine developers/manufacturers, regulators, NGOs and in cooperation with WHO are highly demanded to develop international standards.

Biosketch

Laurent Mallet

Head of Biological Standardisation, OMCL network & HealthCare (DBO) Department
Strasbourg, France
European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe

Tel: +33 3 90 21 48 55
E-mail: laurent.mallet@edqm.eu

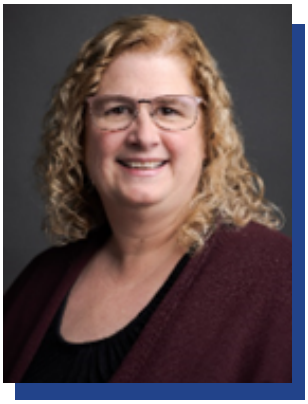
Dr. Laurent MALLET obtained his Master Degree of Science in Biochemistry from Claude Bernard Lyon University in France. He completed his PhD work in Virology and Molecular Biology under the co-direction of Pr Michèle Aymard (National Reference Center for Enterovirus, Lyon, France) and Dr. François Pelloquin (Sanofi Pasteur, formerly Pasteur Mérieux Connaught). He obtained his PhD in 1996. After several positions within Sanofi Pasteur in France and in Canada, he has been the Global Head of Analytical Sciences within Sanofi Pasteur up to November 2019.

Since December 2019, he has joined the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, in Strasbourg, France. At EDQM, he is currently the Biological Standardisation, OMCL Network & HealthCare (DBO) Department Head.

He has been a member of several expert committees such as the EDQM Group 15 "Human vaccines and sera" at European Pharmacopoeia. In addition, he has been involved in several WHO working groups on vaccines including the WHO Study Group on Cell Substrates.

In his role, he represents EDQM in the WHO Expert Committee on Biological Standardization (ECBS), in the NC3Rs working group to review animal testing requirements in WHO biologicals guidelines, in the COVAX Regulatory Advisory Group, in the IABS Board and in the ICH Q5A Expert Working Group.

Biosketch



Diane McCarty

Senior Director, Global Biologics
20852 Rockville, MD USA
United States Pharmacopeia
20852 Twinbrook Parkway

Tel: +1 (301) 692-3637
E-mail: diane.mccarthy@usp.org

Dr. McCarthy is Senior Director, Science and Standards in USP's Global Biologics Department, where she leads development and maintenance of physical and documentary standards to support quality of medicines and oversees the USP biologics laboratories in the US and India. Her team supports standards and tools across a diverse range of therapies, including vaccines, peptides, cell and gene therapy, monoclonal antibodies, and other protein therapeutics.

Prior to joining USP, she worked for several small CROs that focused on the characterization of biologics, host cell proteins, and biomarkers. Dr. McCarthy earned her Ph.D. in Biochemistry from the University of Texas at Austin.

Abstract

Diane McCarthy

The Future of Reference Standards for Vaccines

Diane McCarthy, United States Pharmacopeia

Background: Reference Standards have played a critical role in development and quality control of vaccines for over 100 years. For vaccines, these have traditionally been product-specific and focused on assessing bioactivity and critical assay reagents.

Challenges: The COVID-19 pandemic revealed challenges in ensuring vaccine quality, consistency, and availability. It exposed existing vulnerabilities in the supply chain and emphasized the need for a consistent supply of high quality raw and starting materials. The need to respond rapidly to emergence of new variants also challenged traditional paradigms for analytical testing and standard development.

Proposed Approach: An expanded portfolio of novel reference materials could alleviate many of these challenges by providing a benchmark to support analytical testing. Three case studies will be presented to illustrate approaches USP is taking to expanding our portfolio of reference standards and materials to support analytical testing across the entire vaccine development lifecycle:
1) Reference Standards for Raw and Starting materials: CRM197, a carrier protein used in conjugate vaccines, is produced using multiple manufacturing processes and is susceptible to cleavage. Our approach to developing a Reference Standard for CRM197 to support qualification of raw materials will be discussed.
2) Reference Standards for Platform Analytical Methods: mRNA-based vaccines have common physiochemical properties, making them amenable to platform analytical methods. Our vision and considerations for development of platform-based reference standards will be shared.
3) Reference Standards of the Future, Digital? Modern analytical methods like NMR and mass spectrometry could enable development of digital standards for vaccines. We will discuss USP's experience with this approach for small molecules and challenges for adapting it to vaccines.

Conclusions: The need for flexibility and speed, coupled with high quality, has resulted in increased emphasis on quality assessment of raw and starting materials and on increased use of platform analytical methods. New approaches to vaccine reference standards are needed to support expanded industry needs.

Biosketch

Catherine Milne

Head of Section, BSP/ISA/OCABR, DBO
European Directorate for the Quality of Medicines & HealthCare (EDQM)
Strasbourg, France

E-mail: catherine.milne@edqm.eu

Catherine Milne received her doctoral degree from the University of Toronto, Department of Molecular and Medical Genetics and was a post-doctoral fellow at the Medical Research Council, Laboratory of Molecular Biology in Cambridge, England in the field of molecular genetics and developmental biology. She joined the Council of Europe, European Directorate for the Quality of Medicines & HealthCare (EDQM) in 1999 to work in the fields of Official Control Authority Batch Release (OCABR) and biological standardisation. She is now head of the section covering activities in biological standardisation, international standards for antibiotics (ISA) and OCABR of human and veterinary vaccines and medicinal products derived from human blood and plasma. In her role as EDQM Biological Standardisation Programme (BSP) administrator, she coordinated a number of projects for the establishment of reference standards and methods for the evaluation of human and veterinary biologicals with a focus on the 3Rs. She represents EDQM as an observer at the EMA BWP, CAT and the 3Rs Working Party and is a member of the IABS VBC.

Abstract

Catherine Milne

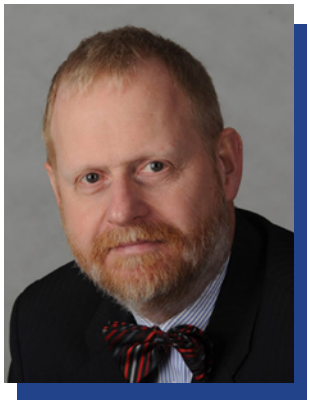
An overview of the contribution of reference standards to the quality control of vaccines

Catherine Milne, European Directorate for the Quality of Medicines & HealthCare

The quality of medicines, including vaccines, is of critical importance to their safety and efficacy for the end user. The ability to produce consistent batches of the appropriate quality, in line with batches found acceptable in the clinic, should be an integral part of production and control strategies for medicines. Reference standards have long played a key role in these control strategies. The control of biologicals, like vaccines, has historically faced challenges linked to the inherent variability in starting materials, the products themselves and the test methods used to control them. The very definition of biologicals reflects this i.e. 'substances which cannot be fully characterised by physico-chemical means alone, and which therefore require the use of some form of bioassay'[1]. Without the ability to use a defined metrological unit, content/potency/activity in a biological assay has traditionally been compared to a reference standard with some defined unit, the first of which is usually assigned arbitrarily. The advent of International Standards (IS) from the World Health Organisation and use of the International Unit (IU), a common basis for the 'arbitrary' unit, was a great step forward. Use of these standards and units has been an essential part of ensuring vaccine quality in the past decades. The IU allows calibration of secondary standards, like common regional standards, established by organisations such as the European Directorate for the Quality of Medicines and HealthCare, US FDA and others, or in-house standards, by providing a common, externally verified basis of comparison. The presentation will include a look back at the history of reference standards and their use and their contribution to maintaining the quality of biological medicines like vaccines.

[1]WHO/IVB/11.03: WHO manual for the establishment of national and other secondary standards for vaccines

Biosketch



Pieter Neels

Ex-CHMP member, Ex-EMA Vaccine Working Party Vice-chair, Vaccine-Advice BVBA Founder
Ex-Associate Professor University of Namur

Chair – Human Vaccine Committee
Ex officio member – Executive Committee

Dr Pieter Neels is a native of Belgium where he trained as an MD (University of Antwerp, 1985) and was boarded as a general practitioner. In 1994, his interest for medical research led him to work for a pharmaceutical company.
In 1997, he joined the Belgian Ministry of Public Health as a senior evaluator of the clinical part of registration files in the field of cardiology, nephrology, endocrinology (diabetes), ...

In 2001 he was appointed CPMP member. In 2002 he was asked to take over all Belgian central vaccine rapporteurships. During this year he became infected by the world of vaccines and until June 2013 he was the rapporteur of more than 15 vaccines.

After being an observer for more than 5 years at the Vaccine Working Party, he was elected vice-chair of this CHMP Working Party for discussion on development and evaluation of registration files for vaccines until June 2013.

The Belgian agency started a spearhead policy in 2007 and Dr Neels was appointed co-ordinator for the spearhead domain vaccines.

EMA/CHMP has asked Dr Neels has be an observer at the SAGE/WHO meetings and to attend several scientific meetings on vaccines until June 2013.
WHO has asked Dr Neels to attend many meetings on vaccine development all over the world in order to share the EU regulatory requirements/competence in vaccinology.

Biosketch
Pieter Neels

Dr. Neels is also a member of the worldwide network on vaccine promotion as he is asked to attend the ADVAC course (Foundation Mérieux) and the IABS conferences.

In 2013 Dr. Neels was nominated associate Professor at the Namur University for a course in Vaccinology, in 2020 dr. Neels retired as associate professor at the university.

In June 2013 Dr Neels stepped down from the CHMP and left the Belgian Federal Agency to start his own consultancy company "Vaccine-Advice" in order to be able to support vaccine development in a more efficacious way.

In 2014 Dr Neels was elected board member of IABS-EU and in 2016 he accepted to chair the Human Vaccine committee of IABS.

Biosketch

Shawn Novick

E-mail: Novicksl@hotmail.com

Shawn Novick graduated from New York University and has been working in various positions in the Biotechnology industry for over 30 years, primarily focused on analytical development, characterization, and quality control. She has worked on several clinical and commercial products, including mAbs, ADCs, and other therapeutic proteins.

Currently Shawn is a consultant with BioPhia Consulting and is Chair of the IABS Biotherapeutics Committee.

Biosketch

Sandra Prior

Principal Scientist
Medicines and Healthcare products Regulatory Agency (MHRA)
United Kingdom

E-mail: Sandra.prior@nibsc.org

Sandra Prior joined the National Institute for Biological Standards and Control (NIBSC), a center of the Medicines & Healthcare Products Regulatory Agency (MHRA, UK), in 2015. She works as a principal scientist in the Science, Research and Innovation group, investigating structure-function in relation to the safety and efficacy of monoclonal antibody products and developing international standards for biotherapeutic monoclonal antibodies, establishing the first WHO international standard for this type of biological medicines in 2017.

She also contributes to vaccine immuno-monitoring and clinical assessment activities. She is a member of the European Directorate for the Quality of Medicines and HealthCare (EDQM) monoclonal antibody expert committee and the Official Medicines Control Laboratory (OMCL) monoclonal antibody testing group.

She obtained her PhD from the University of Navarra (Spain) and moved to the UK, where she initially worked at NIBSC investigating safety and protective mechanisms of bacterial combination vaccines. In 2010, she joined Lonza Biologics (Cambridge, UK) working on bioactivity and immunogenicity assessment of candidate biotherapeutics. Sandra has over 20 years of experience in applied immunology and in vitro cell-based assay development.

Abstract

Sandra Prior

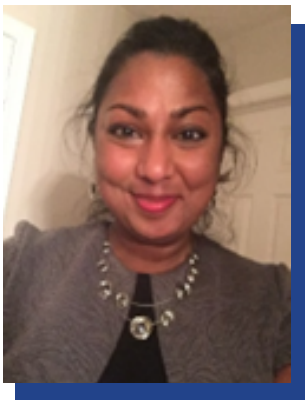
The role of International Standards for Monoclonal Antibodies in supporting bioassay data harmonisation: perspectives from the human biotherapeutics field

Sandra Prior, MHRA

Biotherapeutic monoclonal antibodies provide treatment to many oncological, immunological, and infectious diseases. A robust regulatory framework, facilitated by state-of-the-art analytical methodologies and the improved understanding of product heterogeneities, has enabled the approval of more than 30 biosimilar monoclonal antibodies in the last few years, increasing global patient accessibility to these medicines. Although analytical development and increased knowledge have leveraged their successful regulatory approval and control, ensuring consistency in a rapidly expanding and complex marketplace emerges as a new regulatory challenge. Further, various mechanisms of action typically contribute to the clinical therapeutic effects of monoclonal antibodies, but often in ways not fully understood. Therefore, there is a clear need to develop tools to assess the potential drift and divergence in the various biological activities for different monoclonal antibody products overtime and across jurisdictions.

International Standards have contributed to the harmonization of biological medicines for over a century. The development of International Standards for monoclonal antibodies represents a significant milestone as a new type of international standard and an addition to the tools available to ensure consistency in the potency of different versions of the same product. However, understanding their unique role is essential to fully realize their potential in supporting bioactivity traceability horizontally (across different products) and longitudinally (over the products' life cycle). Appreciating the differences between the international standard and the reference medicinal product that is required for biosimilar approval and breaking through common misconceptions are key discussions.

Biosketch



Gayle Pulle

Manager, Vaccine Quality Division
Health Canada
Ottawa, ON, Canada

E-mail: gayle.pulle@hc-sc.gc.ca

Gayle Pulle received her doctoral degree from the University of Toronto, Department of Immunology and then completed a post-graduate degree certification in Regulatory Affairs & Quality Control from Seneca College. She joined Health Canada as and Evaluator for Quality Control of vaccines and has been with this regulatory agency for 15 years. She is now manager of one of the three Vaccine Quality Divisions.

In her roles, she has reviewed and made decisions on submissions qualifying and re-qualifying reference standards, supervised lot release potency testing of vaccines using reference standards, and has also participated in international collaborative studies for calibrating new international reference standards. She is also been a member of the NC3Rs international working group with a focus on the 3Rs.

Abstract

Gayle Pulle

Regulatory Perspectives on Reference Standard Management Protocols for Vaccines

Gayle Pulle, Health Canada

Background: Reference standards are used to calculate test results of relative assays or as acceptance criteria for assay control, and they play an important role for the control of critical vaccine quality attributes. Vaccine reference standards are typically biological materials and may undergo confirmation changes or degrade during storage. This makes the appropriate management of reference standards and their replacements a key strategy to ensure that the critical quality attributes of commercial vaccine batches manufactured throughout product lifecycle remain comparable to materials shown to be safe and efficacious (or immunogenic) in clinical studies.

Challenges: Comparability protocols need to be in place to assess whether the reference standard continues to be fit for its intended purpose. Working reference standards are initially assigned an expiry date but this shelf-life is reassessed as standards are monitored over time. Predicted data is often based on statistical modelling approaches; however, this can be difficult to interpret. Depending on the assay, significant trends as defined by p values may not be scientifically meaningful. Alternatively, it may be difficult to define trends for an inherently variable in vivo assay.

Approach Being Taken: Appropriate comparability protocols should be in place to ensure governance of these reference standard and shelf-life extensions. These protocols should include re-evaluation criteria, justification of acceptance criteria that is scientifically sound for both qualification and requalification, historical data and assumptions used in statistical approaches; how to evaluate trends in performance of reference standards; and maximum assigned re-evaluation dates. In order to downgrade regulatory reporting categories, post-approval change protocols for reference standards require sufficient details to ensure appropriate control of these critical materials are maintained.

Conclusions: In the context of ICH Q12, harmonization of approaches for comparability protocols and consistency in guidance to manufacturers would aid in a better designed reference standard management system. This would also then lead to less regulatory burden over the lifecycle of the product.

Biosketch

Peter Rigsby

Head of Biostatistics,
Science Research & Innovation Group,
Medicines and Healthcare Products Regulatory Agency (MHRA),
United Kingdom

Tel: +44 1707641286
E-mail: Peter.Rigsby@nibsc.org

Peter Rigsby has over 25 years' experience as a statistician in the application of statistical methods in international studies of biological reference materials. He currently works in the Science Research and Innovation group at the Medicines and Healthcare Products Agency (MHRA) where over 95% of World Health Organization (WHO) International Standards and biological reference materials are produced.

He obtained his undergraduate degree in Mathematics from the University of Oxford in 1995 and his MSc in Biometry from the University of Reading in 1996, joining the National Institute for Biological Standards and Control (NIBSC) in 1997. As a fellow of the Royal Statistical Society (RSS), he gained his Chartered Statistician (CStat) qualification in 2002.

Abstract

Peter Rigsby

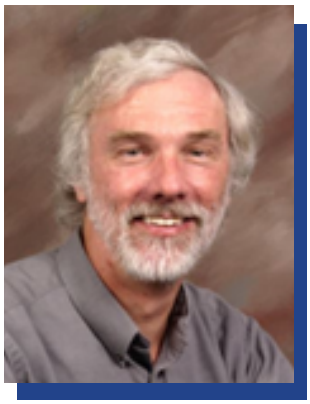
Current approaches in the establishment of International Reference Standards for Vaccines

Peter Rigsby, National Institute for Biological Standards and Control

World Health Organization (WHO) International Standards (IS) are biological reference materials that support a wide range biological medicines, including vaccines. These IS are considered to be the 'gold standard' against which regional, national and international laboratories and manufacturers should calibrate their own working standards. They are calibrated in units of biological activity and the processes to develop such standards typically includes an international collaborative study with multiple laboratories and assay methods. Proposals resulting from such studies regarding an assigned potency for the IS and its intended use are discussed and endorsed by the WHO Expert Committee on Biological Standardisation (ECBS) before formal establishment and availability to users.

An overview of the challenges and issues encountered during the establishment process will be presented, including appropriate collaborative study design and analysis, calibration and unitage assignment to new and replacement standards, the assessment and prediction of stability and the evaluation of commutability. Current approaches will be presented, such as the inclusion of representative test samples in the collaborative study to assess commutability and stability assessment using accelerated thermal degradation samples of the candidate standard. The limitations of these approaches and issues arising from their use will be discussed.

Biosketch



Tim Schofield

Owner & Consultant
CMC Sciences, LLC
Maryland, USA

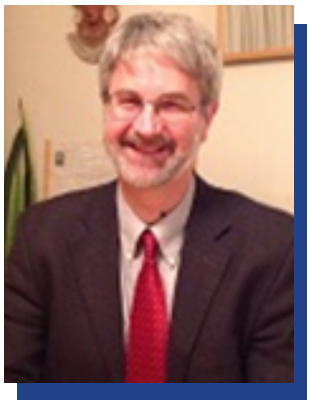
Tel: +1 (240) 654-2867
E-mail: tim@cmcsciences.com

Tim Schofield is the Owner & Consultant at CMC Sciences, LLC. Prior to starting his own consulting business Tim worked at:

- GSK as a Senior Advisor in Global Vaccines Technical R&D, and previously a Director in US Regulatory Affairs,
- MedImmune as a Senior Fellow in Analytical Biotechnology,
- Arlenda as US Managing Director and Head of Nonclinical Statistics, and
- Merck Research Laboratories heading the Nonclinical Statistics department.

Tim received a Bachelor of Science degree in Mathematics from Lafayette College, and a Master of Arts degree in Statistics and Operations Research in 1976 from the Wharton School of the University of Pennsylvania. Tim is a member of the USP Statistics Expert Committee and has participated in industry initiatives related to Quality by Design, analytical method development and validation, stability and specifications. He is the Chairman of the IABS Communications Committee, and on the editorial board and is the business lead for the journal Biologicals.

Biosketch



Dean Smith

Ph.D.

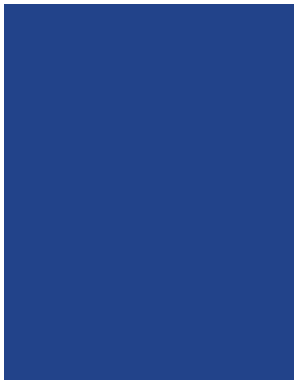
Tel: +1 613-799-5689
E-mail: dean.smith@hc-sc.gc.ca

Immunologist and A/Manager of a Vaccine Quality Division and Advisor in the Center for Vaccines, Clinical Trials and Biostatistics at Health Canada. Dr. Smith has over 20-years of experience in regulatory science in support of innovation in vaccine development, manufacturing and quality control. He has a wide range of biologics-based scientific and regulatory experience from his Senior Scientific Evaluator and management roles in Centre Divisions including Viral and Bacterial Vaccines, as well Hemostatic Agents and Blood Substitutes.

Representing Health Canada, Dr. Smith contributes to WHO's vaccine and vaccine stability guidance development initiatives and supports WHO's recent efforts with COVID-19 and Monkeypox vaccine responses. He is Health Canada's representative to the European Directorate of Quality of Medicines (EDQM), Group 15 (Vaccines and Sera) in support of the European Pharmacopeia, the Regulatory Advisory Committee to the WHO/Collation for Emergency Preparedness and Innovation (CEPI) and served on the Science and Ethics Advisory Committee for VAC2VAC under the European Vaccines Initiative.

Dr. Smith's Ph.D. in Immunology is from the University of Alberta, Canada, where his research dealt with vaccine antigen discovery, autoimmunity and viral vector-based gene therapy. He was a Research Associate at the National Research Council's Institute of Biological Science, Vaccine Design Group in Ottawa prior to joining Health Canada.

Biosketch



Geetha Srinivas

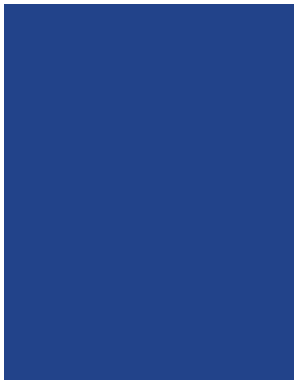
Supervisory VMO Organization / Company : USDA APHIS VS
Address: Ames, IA 50010

E-mail: geetha.b.srinivas@usda.gov

Dr. Geetha Srinivas received her D.V.M. degree from the College of Veterinary Medicine, Bangalore, India. She continued her graduate degree at the VA-Maryland regional college of Veterinary Medicine, University of Maryland, College Park, Maryland, and received her M.S. degree in Virology and Immunology with research focused on Newcastle disease virus. She earned her Ph.D. in 1995 in Veterinary Microbiology and Immunology.

Dr. Srinivas started her career with a licensed biologics firm, Fort Dodge Animal Health in 1996. She managed the Virology Section in the Department of Product Development. She later joined the Center for Veterinary Biologics in 2003 as the biologics product reviewer, and currently Heads the Virology and Molecular Biology Section in the Policy, Evaluation, and Licensing Unit of the Center for Veterinary Biologics, USDA in Ames, Iowa, USA.

Biosketch



Paul Stickings

Head of Vaccine Reference Materials
NIBSC South Mimms, Potters Bar, UK
Medicines and Healthcare products Regulatory Agency

Tel: +44(0)1707641054
E-mail: paul.stickings@nibsc.org

Dr Stickings joined the UK's National Institute for Biological Standards and Control (now the UK Medicines & Healthcare products Regulatory Agency) in 2005 where he has been responsible for the independent batch release testing of bacterial vaccines and the development of biological reference materials. Research interests have focused on the development and validation of cell based assays for bacterial toxins and immunochemical assays for toxoid vaccines, as well as development of novel therapeutic monoclonal antibodies.

He is currently Head of Vaccine Reference Materials and has led multiple International collaborative studies leading to the establishment of WHO International Standards and is a temporary adviser to the World Health Organization on vaccine control and standardization. He is a member of the European Pharmacopoeia Commission Expert Group on Vaccines and Sera and the United States Pharmacopoeia Expert Committee on Complex Biologics and Vaccines.

Abstract

Paul Stickings

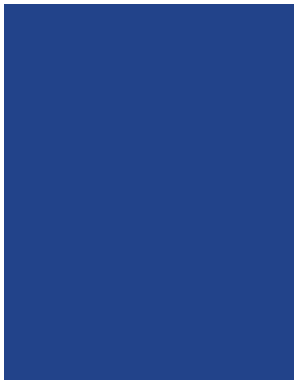
Challenges when assessing multi-component vaccine formulations

Paul Stickings, MHRA, UK

Background: In vivo Potency assays are used for routine batch release testing for many vaccines. The variability that is inherent in many bioassays can be significantly reduced by the inclusion of a reference standard in the assay, with measurement of the biological response expressed in relative terms. Well characterised, stable reference materials are established as WHO International Standards based on evidence that they improve agreement between laboratories in one or more assay models. For some vaccines, this has facilitated the development of internationally agreed minimum criteria for potency that is applied during routine control testing.

Challenges: Biological standardisation is underpinned by the concept of comparing like vs. like, since valid relative potency estimates are dependent upon achieving an acceptable degree of parallelism between the reference vaccine and the test vaccine. The complexity of many vaccine products – in terms of the number and type of components and adjuvant used – means that there may be significant qualitative differences between the International Standard and the test vaccine. This can pose challenges either in routine testing or when transferring the unit of activity to a local standard in a calibration exercise, making it difficult to manage a local reference standard programme that is traceable to the International Standard. Qualitative differences between the reference standard and the test vaccine can also lead to discrepancy in results obtained for the same sample tested in different laboratories (or assay models). This case study will present some examples of these challenges and the implications for using common acceptance criteria for potency across different product types.

Biosketch



Catrina Stirling

Biosketch

Mária Szabó, DVM

World Animal Health Organisation (WOAH)
AMR and Veterinary Products Department,
12 rue Prony, Paris, France 75017

Tel: +33 (0)1-44 15 18 88
E-mail: m.szabo@woah.org

Dr Mária Szabó obtained her veterinary degree at the Veterinary Science University in Budapest. After some years in Human Neuroscience Research, she worked in the veterinary field.

Before she joined the WOAH (OIE), she was employed in a vaccine producing multinational company, Ceva-Phylaxia Co Ltd, working as the lead expert on European procedures.

Previously she worked in the Hungarian public sector, as part of a regulatory body known as the Directorate of Veterinary Medicines, for nearly 15 years. During that time, she was seconded to London for two years as a National Expert to the European Medicine Agency (EMEA). She acted as a secretary to the Veterinary Mutual Recognition Facilitation Group (VMRFG), (later the Co-ordination Group for Mutual Recognition and Decentralised Procedures, (CMDv), to the Committee of Veterinary Medicinal Products (CVMP)-Environmental Risk Assessment Working Group (ERA-WP), and as a project manager for centralised procedures. She represented Hungary in different international forums in terms of veterinary medicines. Since 2015, Mária has been working for the Word Organisation of Animal Health (WOAH), based in Paris. She was responsible for the mission of veterinary medicinal products, now working as a scientific coordinator.

Abstract

Glen Gifford & Mária Szabó

WOAH* Procedures for Development, Validation and Adoption of Standards for Veterinary Vaccines and Reagents
*Founded as OIE

Background: The World Organisation for Animal Health (WOAH, founded as OIE) is an intergovernmental standard-setting organisation that develops and implements animal health technical standards, including standards for vaccines and diagnostic tests, and capacity building programs, through a global network of Members and experts in Reference Laboratories and Collaborating Centres. WOAH standards are developed, validated, and adopted by Members in a science-based, transparent, democratic procedure. Once adopted, the standards are published in WOAH Codes and Manuals, which are applicable for all WOAH Members and become the internationally agreed basis for trade, under the World Trade Organization Sanitary & Phytosanitary (WTO SPS) Agreement.

Challenges: WOAH and the Food and Agriculture Organisation of the United Nations are jointly engaged in a comprehensive vaccination and testing program to control and globally eradicate a disease of sheep and goats, peste des petits ruminants (PPR), by 2030. The participating vaccine manufacturers, animal health workers and farmers in PPR infected regions of Africa, Middle East, Asia and Europe require timely access to safe and effective vaccines that conform to international quality standards, as published in the WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual). The PPR Global Eradication Program (PPR GEP) will require large scale production of conventional modified live PPR vaccines, as well as specialized vaccines, diagnostic tests, and reagents, such as: (1) vaccines with well characterized or enhanced thermotolerance properties for use in regions where the cold chain may be interrupted; (2) 'DIVA' vaccines and corresponding diagnostic tests for differentiating infected animals from vaccinated animals; and (3) clearly defined quality assurance standards for PPR vaccines to help ensure that manufacture consistently provide high quality vaccines while also conforming to the 3R principles for refining, reducing and replacing use of animals for laboratory testing and (4) PPR diagnostic tests and reference reagents for use in vaccine production and quality control.

Conclusions: To address animal health stakeholders' ongoing needs, including those of the PPR GEP, the WOAH continuously updates the relevant Terrestrial Manual standards for vaccines, diagnostic tests, and reagents. The slide presentation will review the key challenges and discuss some recent actions that have been undertaken to address them.

Biosketch

Sylvie Uhlrich

Global head Analytical Sciences
69280 Marcy l'Etoile, France
SANOFI Vaccins
1541 avenue Marcel Merieux

Tel: +33 43737 9513
Mob: +33 63053 2750
E-mail: sylvie.uhlrich@sanofi.com

Dr Sylvie UHLRICH received her PhD in Biochemistry from University of Paris and developed her carrier in Analytical sciences and assay development first in a biotech company and then at Sanofi Vaccines during more than 25 years.

All along her carrier, she has been deeply involved in the introduction of novel analytical technologies and development of 3Rs alternative approaches for Diphtheria, Tetanus, Pertussis, Hepatitis B, Hepatitis A and Rabies vaccine while ensuring scientific and regulatory relevance of analytical strategies for commercial and new vaccines under development.

She is currently Global head of Analytical Sciences at Sanofi Vaccines R&D (based in Lyon), Expert at European Pharmacopeia group 15 (Human Vaccines & sera).

Abstract

Emmanuelle Coppens & Sylvie Uhlrich

Experience on the implementation and the use of reference standards for human vaccines potency testing

Sanofi Vaccines, Marcy l'Etoile, France

As an introduction, general practices at Sanofi Vaccines for the choice and qualification of reference standards will be described as well as their stability monitoring. A focus will be made on qualification study design in the frame of the replacement of a reference standard.

Two case studies on Tetanus in vivo potency and Polio D antigen assays, where a change to a new IRS (International Reference Standard) showed an impact on product consistency with risk of out of specification results, will be shared. For each case, a similar root cause was identified related to the methodology for assigning the titer of the IRS. A common remediation plan based on the implementation of an in-house reference will be presented.

General recommendations on the establishment of IRS will be made. The respective use of an IRS or in-house reference standard will be discussed.

This work was funded by Sanofi.
Emmanuelle Coppens and Sylvie Uhlrich are Sanofi employees and may hold shares and/or stock options in the company.

Biosketch

Wim Van Molle

Quality Assessor and Vaccine Release Responsible
Sciensano, Division Quality of Vaccines and Blood Products
J. Wytsmanstraat 14, B1050 Brussels, Belgium

Tel: + 32 (0)2 642 5652
E-mail: wim.vanmolle@sciensano.be

Dr Wim Van Molle is working at Sciensano, Belgium, in the division of Quality of Vaccines and Blood Products, where he is responsible for vaccine batch release and evaluation of the quality part of registration and variation dossiers of vaccines and biologicals. Wim is involved in scientific advice procedures at national and European level and participates as product expert in GMP inspections on the request of the Belgian (FAMHP) and European (EMA) medicines agency. Dr. Van Molle is actively involved in European IMI projects.

At Sciensano, he is manager of the unit for Cellular and Molecular Biology and Biochemistry, involved in quality release testing of vaccines and blood derived medicinal products.

Wim works as auditor for the European Directorate for the Quality of Medicines & Healthcare (EDQM), Strasbourg, France where he is frequently asked to participate in mutual joined audits of European control laboratories. He is also member of the Ph. Eur. Group 15 on Vaccines and Sera and recently joined the mRNAVAC working party at the EDQM. He is also in firm collaborations with the World Health Organization (WHO) as temporary advisor in the framework of the regulatory strengthening of regulatory authorities and Product Summary File evaluation.

Dr Van Molle holds a Master in Biotechnology and obtained a PhD in Molecular Biology from the University of Ghent, Belgium and worked for over 10 year in the academic field, followed by a 2 year period at the Belgian regulatory authority before joining Sciensano.

Abstract

Wim Van Molle

Regulatory expectations on the use of vaccine reference standards for maintaining product quality

Wim Van Molle, Koen Brusselmans and Lorenzo Tesolin

Introduction: The manufacture of vaccines often involves complex processes requiring a strict control strategy at all steps. The Final Drug product should meet all requirements regarding safety and efficacy before its release to the market. The use of (international) reference standards or reference preparations plays a key role in assay validation and product qualification.

Challenges: Manufactures are sometimes faced with the challenge to select, produce and qualify suitable standards for their intended use. Ideally, international reference standards are developed that can be used worldwide independently of the brand of the vaccine and this both by manufactures as well as by National Control Labs. In case international standards are not (or in limited quantities) available, the use of suitable and properly qualified in-house standards is a valid alternative, but additional qualification requirements might apply.

Relevant Guidance: The requirements for reference standards are greatly determined by their intended use. Different requirements are applicable for a reference standard used for assay validity versus a reference standard used for final lot qualification, especially if it is an assay to determine the potency or activity of the vaccine. In the latter case, it is important that the candidate standard has a clear link with clinical batches that were shown to be safe and efficacious. In any case, when standards are being qualified, the set of release tests should be accompanied by a set of additional characterization assays. Special requirements should be taken into account when in-house reference standards are qualified against internal reference standards and when newly proposed primary or secondary standards are bridged against existing standards.

Conclusions: It is obvious that reference standards play a very important role in the control strategy of vaccines. The requirements for selection and qualification of standards depend on their intended use. The more international reference standards become available and are used, the more harmonization in quality control by companies and authorities can become a reality.

Biosketch

Delphine Vanham

Analytical Industrialization Leader and Subject Matter Expert for analytical materials management
1330 Rixensart, Belgium
Vaccines Technical R&D at GSK

Tel: +32479105964
E-mail: delphine.e.vanham@gsk.com

Delphine Vanham is a Chemical and biotechnical engineer from the University of Louvain-la-Neuve, Belgium specialized in molecular biology and biochemical techniques. She has occupied several positions since she joined GSK in 2006. Firstly, she focused on process evaluation and validation activities during development phases in the Technical R&D department. Then, within the Quality Control department, as product manager, she coordinated product specifications and stability management and contributed to submission of several new vaccines.

Today, she works within the Analytical R&D department, as Analytical Industrialization Leader and is in charge of defining and leading the implementation of best-in-class, phase appropriate and breakthrough analytical lifecycle approaches as wells as strategies for implementation in commercial QC. She is also the Analytical R&D subject matter expert on analytical material management including reference standards.

Abstract

Marie-Claire Beckers, Geoffrey Duby & Delphine Vanham

Case study: Human vaccine in vitro relative potency reference standard qualification in ELISA

Background

GSK is a global biopharma company with a purpose to unite science, technology, and talent to get ahead of disease together and is a major actor in the human vaccine supply world.

Challenges

Qualification of in-house biological reference standards used in in vitro relative potency ELISA test for release of new human vaccine material is complex to manage:
• No international reference standards are yet available.
• The limited initial reference standard stock leads to the need of managing multiple changes prior to identifying the primary/gold reference standard.
• The stability data package of the initial representative material is often limited (less than 5 years) at the time of regulatory submission.
• Changes of reference material during method lifecycle require an agreement from multiple different authorities which leads to a complex implementation strategy.
• Challenge for transferring Quality Control materials to National Control Laboratories or to other sites with relevant and complex importation requirements.

Proposed approach being taken

We propose to share a practical case-study of in-house biological reference standard qualifications and managements.
• Two approaches will be presented to define how an antigen content value can be determined: using either an absolute orthogonal method or using an antigen specific content method. In addition to the antigen content, the potency value of the primary/gold reference standard, representative of Phase III and supporting the efficacy of the vaccine, is assigned to 100%.

Abstract

• To support the change of working reference standard lot, instead of using a two-tiered approach to bridge each reference standard to the primary reference standard, we propose the use of a one-tiered approach considering the successive comparability of the new reference standard versus the current one. Based on the product and process knowledge, the difference between new and in-use reference standards is expected to fall within a pre-defined interval depending on the method performance and therefore a 100% potency will be assigned to the new reference standard. This approach circumvents the impact of some potential stability evolutions and error propagation inherent to the application of corrective factor.
• Finally, to facilitate the lifecycle management and anticipate the change of reference standards, pre-approved qualification protocols are shared with authorities allowing to smooth and accelerate the new reference standard implementation.
• With a continued growth of vaccines in the coming years, we propose to improve the robustness of the transfer process to cope on the specific demands of National agencies and the importation process.

Biosketch

Swati Verma

Regulatory Scientist (Biologist)
10903 New Hanpshire Avenue, Silver Sprin,
Maryland USA
Food and Drug Administration

Tel: +1-240-402-7449
E-mail: swati.verma@fda.hhs.gov

Dr. Swati Verma is working as a Regulatory Scientist (Biologist) in the Division of Viral Products in the Office of Vaccines in Center for Biologics Evaluation and Research at FDA. She received her PhD in Biotechnology in 2013 from Banasthali Vidyapith University in India. She is a virologist by training.

She is actively involved in regulatory review and oversight as a Chemistry Manufacturing and Control (CMC) expert for viral vaccines, including novel mRNA platform-based COVID-19 vaccines from early phase of development through final authorization or licensure. She has expertise in biological and immunological assays that are used for the assessments of product quality and evaluation of immune response generated following vaccine administration.

Abstract

Swati Verma

Use of Reference Standards to Monitor Product Quality: US FDA perspective

A biological standard is a reference material which is rigorously characterized using relevant biological assays. There are different types of standards and terminologies used but all are essentially used for monitoring the quality of a biological product, calibration of assays and/or in the evaluation and harmonization of clinical data across multiple laboratories. The FDA recommends use of high-quality standards to ensure the quality of biological products for public health use.

With regards to vaccine development, early adoption of standard use, as soon as a WHO International Standard (IS) or a NIBSC reference material becomes available, is highly recommended by the FDA. Prior to implementation of an International Standard, an in-house developed reference reagent can be used. Such standards are typically a thoroughly characterized vaccine bulk lot that was used in clinical trials and for which immunogenicity has been demonstrated. Eventually the in-house reference standard or NIBSC standard should be calibrated against the WHO IS when it becomes available.

Standards are used in biological assays to ensure that the assay is performing as designed. Vaccine reference standards are used to calibrate the analytical assays to determine the potency in terms of titer, antigen content, immunogenicity and to provide quality control for manufacturing consistency. Standards are also used for the standardization and harmonization of assay data across different laboratories.

Generally, standards are quite stable, but degradation can occur and therefore it is critical to monitor stability, especially for any in-house developed reference standard. Storage and handling conditions should be defined, and trending analysis of the data from the standards are needed to monitor any shifts in activity. When a standard is near depletion, complete information on the characterization and qualification of a new standard and bridging to the old standard is required.

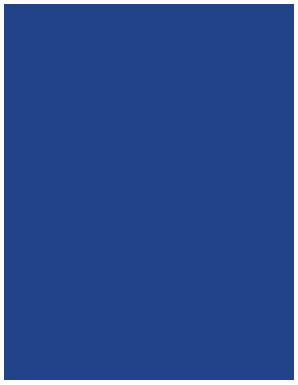
Biosketch

Angela Walker, DVM, PhD

Veterinary Medical Officer, Review Staff
USDA; Center for Veterinary Biologics
Ames, Iowa, USA 50010
1920 Dayton Ave

Tel: +1 515-337-7020
E-mail: angela.m.walker@usda.gov

Biosketch



Esther Werner

Biosketch

Tong Wu

Senior Scientific Evaluator, Vaccine Quality Division 3
Biologic and Radiopharmaceutical Drugs Directorate (BRDD) Health Canada
Ottawa, ON, Canada K1A 0K9

Tel: +613-864-6956
E-mail: tong.wu@hc-sc.gc.ca

Dr. Tong Wu received her Ph.D. in molecular genetics from Chinese Academy of Sciences. She then worked at Georgia State University and Ottawa Hospital (Civic Campus) as a post-doctoral fellow. Her research included the development of DNA vaccines and novel vaccine adjuvants. Dr. Wu joined the Vaccine Quality Division of Health Canada as a Senior Scientific Evaluator in 2005, and is responsible for submission review and lot release of Inactivated Poliomyelitis Vaccine (IPV) and meningococcal vaccines.

Since 2007, Dr. Wu has worked many times as a WHO Temporary Adviser to support WHO in activities related to vaccines, such as preparation of WHO Guidelines as a drafting group member, dossier review for the pre-qualification program, and presentation at workshops for the implementation of WHO guidelines.

Abstract

Tong Wu

Scientific considerations for implementing and maintaining reference standards for the lifecycle management of Vaccines

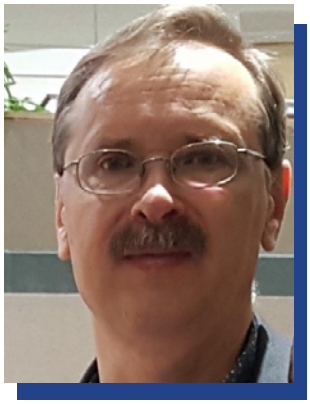
Background: Reference standards are used to calculate test results of relative assays or as acceptance criteria for assay control, and they play an important role for the control of critical vaccine quality attributes. Vaccine reference standards are typically biological materials and may undergo confirmation changes or degrade during storage. Therefore, it is unlikely that the same batch of primary reference standard (including International References) can be stored indefinitely and used to calibrate all future working reference standards. This makes the appropriate management of reference standards and their replacements a key strategy to ensure that the critical quality attributes of commercial vaccine batches manufactured throughout product lifecycle remain comparable to materials shown to be safe and efficacious (or immunogenic) in clinical studies.

Challenges: The aim of reference standard management is to ensure that all reference standards (e.g., the last one vs the first one) are comparable throughout the lifecycle of a product, but this is challenging for several reasons. Firstly, the assays used to qualify reference standards (e.g., ELISA, in vivo immunogenicity assay) have inherent variability and this uncertainty is compounded with the qualification of each successive reference standard. Secondly, the potency of a reference standard is typically expressed in arbitrary units (e.g., IU, DU for IPV), which cannot be monitored or verified independently. Finally, some relative assay readouts (e.g., ED50, CCID50), which have been proposed for monitoring reference standards, are too variable to be useful.

Proposed Approach: Orthogonal methods have been proposed as additional tools to improve stability monitoring of reference standards. However, this approach may not be sufficient if the orthogonal methods use the same reference standard or measure the same quality attribute. Alternatively, the arbitrary unit of a reference standard (e.g., IU) can be directly linked to an alternative quality attribute (e.g., protein content) that can be measured accurately and precisely, and assessment of these quality attributes combined can improve the ability to detect a drift or shift in reference standard potency prior to implementation as a replacement.

Conclusions: Given the critical role that reference standards play in the control of vaccines, a well-designed reference standard management system that incorporate additional monitoring tool, is essential to ensure that a product remains comparable throughout its lifecycle.

Biosketch



Alexander Zakhartchouk

Veterinary Biologics Evaluator
59 Camelot Drive, Ottawa, ON K1A 0Y9 Canada
Canadian Food Inspection Agency

Tel: + 1 343 574 5079
E-mail: alexander.zakhartchouk@inspection.gc.ca

Dr. Alexander Zakhartchouk received his PhD in molecular biology from the National Research Institute of Agricultural Biotechnology (Moscow, Russia) and DVM from Moscow Veterinary Academy. After completing a post-doctoral training at the Vaccine and Infectious Disease Organization (VIDO), Canada, he worked as a Research Scientist at the Crucell company (The Netherlands) and later at VIDO, Canada. He is an adjunct professor in the Department of Veterinary Microbiology at the Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

Dr. Zakhartchouk has been involved in molecular characterization of non-human adenoviruses with the aim to develop them as live vaccine vectors for animals and humans. After the SARS-CoV-1 epidemic occurred, he became involved in developing a vaccine against SARS-CoV-1.

Dr. Zakhartchouk joined the Canadian Food Inspection Agency (CFIA) in 2018 as a Veterinary Biologics Evaluator at the Canadian Centre for Veterinary Biologics (CCVB). The CCVB is responsible for regulating the manufacturing, testing, labelling, import, export, distribution, and use of veterinary biologics in Canada.

Biosketch

Tiequn Zhou

Scientist
Technical Standards and Specifications Health Product Policy and Standards Access to Medicines and Health Products
World Health Organization
Geneva, Switzerland

E-mail: zhout@who.int

Dr Tiequn Zhou joined the World Health Organization (WHO) in 2005 as a scientist in norms and standards for biologicals where she has been engaged in the international biological standardization programme that involves development of international written and measurement standards and standardization of assays to assure the quality, safety and efficacy of vaccines and facilitate international convergence of vaccine regulation.
Providing technical support to regulators, manufacturers and others in countries on the use of these standards is also part of her job. In her role, Dr Zhou has coordinated many standardization activities, through close collaboration with international experts and institutions, including developing guidelines/ recommendations and manual/protocols for various vaccines such as: rotavirus, pneumococcal, meningococcal, yellow fever, poliomyelitis (OPV, IPV), HPV, influenza, Ebola, RSV, and mRNA vaccines. During 2006- 2011, she coordinated a WHO global HPV LabNet tasked for standardization of HPV serology and virology. During COVID-19, she has been engaged in facilitating the development of measurement standards for SARS-CoV-2.

Abstract

Dianliang Lei & Tiequn Zhou

Development and Implementation of WHO measurement Standards for vaccines

Dianliang Lei, Tiequn Zhou, World Health Organization, Geneva, Switzerland

Developing international standards for biologicals and promote their implementation are core functions of the WHO. WHO establishes international measurement standards (IS) through the Expert Committee on Biological Standardization (ECBS), assigning unitage such as International Unit. These standards serve as the primary standard and are used by National Control Laboratories (NCLs) and manufacturers for the calibration of national and other secondary standards, including working standards, for quality control and evaluation of vaccines. They play a crucial role in ensuring the quality, safety and efficacy of vaccines worldwide.
Nowadays, many factors posed challenges to developing and implementing IS, including, but are not limited to:

• new and modern technologies: diverse types of vaccines for a single pathogen and broad range of assays in use may impact on the suitability and applicability of a unified IS.
• assignment of unitage to different types of assays: for example, assigning unitage for antibody-binding assays versus neutralization assays may be complicated.
• fast-evolving epidemiological situation in particular in a public health emergency, like the COVID-19 demands for rapid development of IS to respond to the rapidly changing situation.
• evolving development of vaccines: IS is usually needed and developed at early stage to facilitate vaccine development; however, vaccine development is dynamic and issues may arise when an IS is established after a product is licensed or before a new type of vaccine becomes available.
• need for proper understanding of IS and its use.

Timely development and provision of IS facilitate development, assessment and licensure of biological products, and enable comparability of data across different settings. After the establishment of standards, continuous technical support is crucial to ensure their appropriate use. Ongoing efforts are being made to provide technical support to Member States, targeting NCLs, vaccine developers and manufacturers, which include organizing implementation workshops to elaborate on and promote the use of WHO standards. Global collaboration and synergy among academia, kit and vaccine developers/manufacturers, regulators, NGOs and in cooperation with WHO are highly demanded to develop international standards.

IABS-AFSA Project

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HUMANE SOCIETY INTERNATIONAL

Promoting implementation plans for replacement of animal testing for human vaccines, a project of Humane Society International.

Humane Society International (HSI) is a global animal protection organization that works around the globe to promote the human-animal bond, rescue and protect dogs and cats, improve farm animal welfare, protect wildlife, promote animal-free testing and research, respond to disasters and confront cruelty to animals in all of its forms.
As part of its activities to promote the replacement of animal use, HSI has joined in and initiated a number of dedicated global projects for the replacement of animal use from human and veterinary vaccine batch release testing, engaging and collaborating with leading experts from manufacturers, research organizations, regulatory authorities and national control laboratories.

HSI believes this transition to non-animal based vaccines batch release testing necessary to implement current science with the aim of ensuring products of higher reliability, consistency, faster to release and of potentially lower cost. HSI's effort on the topic joins those of a number of other organizations (VAC2VAC, EDQM BSP, , that in the last 20 years have contributed to the development of new, non animal-based testing approaches for the release of life-saving vaccines and biologicals.

The results of these combined efforts are reflected in the regulatory acceptance and inclusion in regulations and pharmacopoeias of non-animal approaches. But much remains to be accomplished to ensure wider acceptance and the creation of a global regulatory alignment. In particular, efforts need be spent to address the issue of the still limited knowledge of these approaches – in terms of associated challenges, solutions, accessibility of resources – and of the limited awareness of their scientific, economic and public health advantages. The 3-year project "Promoting implementation plans for replacement of

IABS-AFSA Project

animal testing for human vaccines" aims to accelerate the implementation and regulatory acceptance of non-animal approaches for legacy human vaccine batch-release testing with a specific focus on developing countries, advancing the dialogue toward global regulatory alignment while generating local implementation plans and competencies.

Collaboration within local, regional and international industry and regulatory stakeholders is the base of the project's strategy together with knowledge sharing and structured and facilitated dialogue. HSI is engaging all the ex-VAC2VAC members and all the other key experts and stakeholder that operated in the field of replacement, reduction and refinement (3Rs) of animal testing in the last decade and invite them to join the project as subject matter experts.

HSI would like to kindly invite any company or organization to participate in the project with one or more representatives with expertise in quality control, assay development and validation and regulatory affairs for products like Tetanus, Diphtheria, Rabies, Hepatitis A and B, Polio and their non-animal based batch release tests.

Project presentation **Other HSI projects**

For information: Laura Viviani, Project Lead Consultant, SciEthiQ – lviviani@sciethiq.com