Maintaining the quality of vaccines through the use of standards: Current challenges and future opportunities.

Overview

An international hybrid meeting held in Ottawa, Canada on 21-22 June 2023 brought together regulators, scientists, and industry experts to discuss a set of principles and best practices in the development, qualification, and use of physical standards, hereafter referred to as standards. The program included 20 presentations, 3 panel discussions, and a breakout session. For the breakout session, meeting participants were divided into small groups and asked to discuss the following questions:

1. *Based on the discussions at this meeting, what are the biggest challenges for:*
   - *National Regulatory Authorities?*
   - *National Control Laboratories?*
   - *Regional and International Reference Standards setting organizations?*
   - *Vaccine manufacturers?*

   Identify key points that will help address these challenges.

2. *When qualifying a new in-house reference standard used in the QC testing of a vaccine:*
   - *What are the challenges when using an International Reference standard in the calibration/comparability of the new internal reference standard against the previous internal standard?*
   - *Can a vaccine manufacturer ensure comparability of an in-house reference standard and its replacements, independent of an International Reference?*
   - *What are the regulatory expectations regarding the manufacturers' responsibility to monitor the stability and/or ensure the integrity of a reference standard throughout its shelf-life?*

3. *Vaccine development will continue to evolve at an exponential rate, increasing in complexity, diversity, and number of products. Within this context, what principles/concepts can be implemented to ensure reference standards continue to play a key role in ensuring consistency of manufacturing and assay control?*

Summary responses from the discussion groups were presented to the meeting participants prior to the closing remarks. The following represents the conclusions and recommendations that emerged from the meeting.

Conclusions

The first solution for standards emerged in the late 19th century with a recognition that a standard preparation of diphtheria antiserum was necessary to measure the strength of different batches. Standards were subsequently developed for insulin and other biologicals including vaccines. The later development and provision of International Standards (IS) from the World Health Organization (WHO) and use of the International Unit (IU) as a common measure of potency, was a great step forward. Use of these standards and units has been an essential part of ensuring human and animal vaccine quality and consistency in the past decades. However, the type and use of standards has expanded with the development of new technologies leading to a wider range of biological medicines and analytical methods used to assay them, including recent efforts to replace animal-based potency tests with *in vitro* assays to serve as surrogates of clinical efficacy in humans or host animals.

Most legacy vaccines (such as diphtheria, tetanus, pertussis, and rabies) use international standards as calibrators of *in vivo* potency, and some have globally harmonized specifications. With different approaches to vaccine development, maintenance of product quality is evolving with more effort being directed towards developing principles and practices for well characterized internal (or alternative) reference standards rather than using an IS as a direct measure of relative potency. *In vivo* activity assessed in pre-clinical studies and clinical trials allows for the co-development and validation of *in vitro* assays as potential surrogates for product potency. The collective data from these studies informs the establishment of lot release specifications at licensure in a product specific manner and may or may not be linked to international units.

The changing needs of all stakeholders in response to the ever-increasing complexity, diversity and number of vaccine products affords a collective opportunity to further improve the design and implementation of both international and in-house standards. The approval of mRNA-based vaccines in response to the COVID-19 pandemics was acknowledged as the latest paradigm shift in the evolution of vaccine design and has further highlighted the need for a more flexible framework for proper design and use of standards. Concomitantly, greater harmonization of regulatory expectations will be required and the evolving roles of standard setting organizations, national control laboratories, national regulatory authorities, and manufacturers in ensuring vaccine quality through standards program management must be clarified.

Summary Recommendations

- A common set of terminology associated with the different types of standards, their intended uses and the qualification and stability strategies thereof should be developed and adopted globally.
- Standards should be clearly defined and classified by their intended use(s) and corresponding practices should cover chemistry, manufacture, and control (CMC) and bioanalytic applications.
- When a standard is used as a calibrant, its selection, qualification, and stability should consider the relationship to the original assigned value and to the product specification so as to avoid drift.
- The approach taken for assigning units to IS for vaccines, including whether a unitage is necessary, should be carefully considered to ensure that it meets the needs of different stakeholders.
- Additional conferences should be organized to build further consensus, promote scientifically sound changes, and include conversations about the corresponding shifts of responsibility placed upon stakeholders (e.g., financial burdens, specific competencies) that could impact the availability or access of both standards and vaccines.
- The use of working groups, the publication of white papers, and introduction of ideas to promote best practices through other open access distribution channels should lead to ongoing advances in the proper uses of standards. The results of these efforts should be leveraged by regulating bodies, standard setting organizations and others to inform longer term harmonization of official regulations, issued guidance, technical report series, etc.

A comprehensive meeting report reflecting all presentations and panel discussions will be published in the IABS journal *Biologicals* in fall 2023.