International Alliance for Biological Standardization

Maintaining the Quality of Vaccines through the Use of Standards:
Current Challenges and Future Opportunities
Library and Archives Canada, Ottawa, Canada
June 21-22, 2023
Abstract

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., ED_{50}, $CCID_{50}$), 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.