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

Regulatory Perspectives on Reference Standard Management Protocols for Vaccines

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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.