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Substituting In Vitro for In Vivo Vaccine Potency and Safety Assays: Science Versus the Fear Factor

An almost five decade long effort to implement an in vitro alternative to the in vivo NIH rabies vaccine potency assay is but one example of challenges confronting manufacturers, national control laboratories and regulatory authorities in our collective efforts to establish more appropriate and effective in vitro potency and safety quality control (QC) assays for licenced vaccines. In contrast, there are several examples (including adjuvanted viral vaccines and adjuvanted bacterial conjugate vaccines), where key quality attributes are monitored during production and lot release using only physical chemical methods, including or excluding in vitro bioassays. Why then has innovation in assay development for several viral and bacterial vaccines critical public health been such a challenge? While technical issues include the high variability inherent of in vivo methods, an equally important barrier has been an over evaluation of what in vivo assays are capable of and, therefore, a fear of losing these tests. Additionally, there is an undervaluation of the more precise insights into product QC that well-designed in vitro methods can offer. Recently, the European Pharmacopeia (Eur. Ph.) human and veterinary vaccine working groups have developed General Chapter 5.2.14. This guidance introduces "substitution" as a new approach to facilitate the transition from in vivo to in vitro methods, where one-to-one comparisons are not feasible or scientifically justified (e.g., the NIH test for approved products). Eur. Ph. 5.2.14 describes in vivo assays as "less suitable" methods compared to well-designed in vitro QC, strategies and an absence of scientific justification for the General Safety Test resulted in its deletion from the Eur. Ph. Other in vivo so called "safety tests" are being reconsidered. While independently developed, this approach is also in line with subsequent efforts to develop alternative vaccine characterization and QC assays through VAC2VAC under the European-based Innovative Medicines Initiative.

