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Regulatory and Biosafety Challenges for Vaccines

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ABSTRACT

The global regulatory plan for vaccines provides a unique opportunity to develop safe and effective ones with assured quality. Methods used by regulators address challenges of new products and technologies and also increase understanding of benefits and risks of existing products. First, the laboratory-based regulatory sciences evolve correlates of immunity and safety; or improve the product characterization and potency assays. Second, these sciences design clinical trial tools to analyze novel benefit-risk methodologies for vaccines, and standardize regulatory processes. The aim of the Global regulatory agenda is to transform current national efforts into a coordinated execution plan to support worldwide immunization goals. In the current article, it has been defined the role of regulatory science to improved access to effective vaccines, and identified gaps that could be addressed through that. Also, the challenges of implementing a regulatory agenda have been investigated, and proposed strategies to resolve these gaps. In this way, an appropriate agenda will enable regulators, academics and other stakeholders to work in a coordinated way to innovate in the regulatory processes in support of global immunization goals.

Keywords: Vaccine regulation, Vaccine qualification, Vaccine standardization, Clinical trials, Biosafety.

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Introduction

A global regulation can provide unique opportunities to develop vaccine quality, biosafety and efficacy that have been investigated in a limited target population. It is a life-threatening step since the vaccine must protect healthy people and children against a specific disease that they may never get. The global regulatory agenda transforms a current national effort into an organized execution plan to support worldwide immunization goals. The US Food and Drug Administration (FDA) has established a program called Post-Licensure Rapid Immunization Safety Monitoring (PRISM) to improve post-market in situ monitoring based on data from the health and medical service centers **(1, 2)**. Another international program has been undertaken in Europe by VAESCO Consortium (Vaccine Adverse Events Monitoring and Communication) to address specific regulatory and compliance challenges in new products and technologies, as well as the benefit-risk assessments of existing vaccines **(3)**. New vaccines such as recombinant vaccines cannot be disinfected and purified by conventional methods and their validations are entirely dependent on the ability and

reproducibility of bioassays. The biological resources for vaccine production including eggs, mammalian cells or bovine fetal serum are susceptible for contamination. The important features of vaccines to trigger immune response can be enhanced by advancing the quality control of raw materials and diagnostic assays for infectious agents **(4)**.

Materials and Methods

Conventional production processes and their monitoring topics are well-known for viral fermentation and yeast recombinant DNA-based techniques are well-defined **(13)**. However, new vaccines have been produced by other systems including insect cells or live insects **(14)**, transgenic animals or plants, or new cell cultures **(15)**. These systems need specific regulations for the detection of tumorigenesis residual compounds or unfavorable infections **(16)**. Regulatory authorization is the starting point in the production cycle of approved vaccines. When the product is introduced to the market, tests and protocols may change. Any changes to the production process or administration protocol need to be reviewed and approved by the National Regulatory Authorities (NRA). Benefit-risks will be revised and adjusted by monitoring systems, depending on the amount of approved changes or difference between biosafety and efficacy pre- and post-marketing profiles. Laboratory-based sciences design standardized regulatory processes and clinical trials to analyze novel benefit-risk procedures for vaccines. Monitoring guidelines of new production technologies assess immune responses against edible vaccines, or potential growth of insect viruses in humans or animals, alternative antigen phenotypes in new cell cultures with the positive or negative immunogenic effect or residual DNA from host cells. Novel approaches have improved quality and biosafety controls rather than traditional methods. Mass spectrometry, nuclear magnetic resonance (NMR) and circular dichroism (CD) are useful to investigate the final structure of highly glycosylated protein vaccines and their stability, as well as undesirable substances such as bacterial polysaccharides **(19)**. High-throughput sequencing, “next generation sequencing (NGS)”, provides high accurate information about final vaccines, intermediates, substrates **(20, 21)**, or unknown infectious agents for example in a rotavirus vaccine (porcine circovirus) **(22-24)**. By whole genome sequencing, NGS will investigate the genetic stability of viral vaccines containing high mutation rates (such as RNA viruses) **(25)**. Antibody titration can be used to evaluate immunization efficacy and biosafety of new vaccines, adjuvants, or viral strains in seasonal vaccines such as influenza **(28, 27)**. However, it is not sufficient to evaluate intracellular pathogens vaccines with cellular immune responses such as HIV, Tuberculosis (TB), or malaria **(29)**.

Results

The global regulation agenda conducts clinical trials on a large number of healthy volunteers, especially infants and children, for more accurate standardization than other medical products. The regulatory process must be validated for specificity and sensitivity in an international agreement. Development of sensitive and specific assessments are very valuable to predict allergic reactions to vaccine formula or side effects in subpopulations, especially at-risk populations (such as infants). Vaccine biosafety can be improved by providing guidance for at-risk populations to quality control of essential substrates such as human or animal plasma, avoiding transport of infectious compounds; using carefully attenuated immunizations, evaluating toxicity of adjuvants, removing byproducts, and replacing live hosts with tissue cultures for specific vaccines. The number of phase 3 trials and approval time for a new life-saving vaccine should be increased in the absence of a specific biosafety hypothesis for at-risk populations **(30, 31)**. The amount of information required for production stages can be simulated by mathematical modeling and risk predicting **(32, 33)**. In high-risk areas for a disease, people are at greater risk for early vaccination especially for diseases that have no treatment. It seems that further data for the post-market stage give high quality reports quickly and accurately. Reporting systems also play an important role in detecting adverse reactions to vaccine in developing countries that may not have access to electronic medical data. Reports require clinical evaluations as a "case series" to identify irrational patterns **(35)**. However, perfect analysis of reported side effects remains a challenge despite advanced data mining **(34)**. Artificial intelligence can summarize a great deal of information using a variety of algorithmic and statistical methods to obtain similar reports and expert reviews **(36, 38, 39)**. Some successful websites provide public health information about infectious diseases by the least time and cost including "HealthMap" (http://www.healthmap.org/en/) and "Google flu trends" (https://www.google.org/flutrends/about/). Of course, there is a better search opportunity by the epidemics of mobile phone and the like devices. Multivariate criteria decision-making analysis (MCDA) can theoretically be useful to standardize the evaluation of vaccine's benefit-risks in the global guideline as a quantitative model **(40)**. This includes a risk matrix and an uncertainty matrix to visualize key effects for benefit-risk decision making. MCDA facilitates both monitoring and decision-making processes in more complex situations for example multiple contrast effects. By receiving new data, this model will be updated to show alterations in the benefit-risk balances.

Discussion

The appropriate agenda will enable regulators, scientists and stakeholders to work in a coordinated monitoring for global immunizations. Regulatory sciences play important roles in improving biosafety monitoring and investigating strategies to effectively deal with remaining challenges. Vaccine biosafety can be developed by reducing animal use; developing new vaccine evaluations; and verifying high-throughput assays. New approaches to the "success or failure" boundaries of existing experiments must be validated in research laboratories before being approved for regulatory guidelines. The use of samples with different formulation and production process can influence the results. Existing vaccines or even failed ones should be available for new evaluative tests. The creation of one or more international sampling sources provides a mandatory strategy to support global guidelines. WHO partners are expected to mediate the international community to facilitate sample storage and exchange **(48, 49)**. In the past, comprehensive vaccine safety assessments were carried out by major vaccine manufacturers in the United States and the European Union. Currently, the capacity of developing countries has been demonstrated to produce and evaluate its vaccine biosafety, which globally prevents concerns and assures successful vaccinations. However, low-income countries lack the technical resources for accurate biosafety regulation, where other medical problems are mistakenly attributed at the time of vaccination. Therefore, an international guidance by the WHO is essential for the regulation of adverse and rare vaccines reactions in these regions **(53)**.

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Conflict of Interest

Authors declared no conflict of interests.