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**Summary**
Vaccines follow a strict regulatory pathway and the safety assessment is a critical component. The type of studies conducted depend on the vaccine type and it is due to their diversity that they require a case by case approach.

SAFETY ASSESSMENT

# Vaccine Safety Testing Considerations

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Vaccines are subject to distinct regulatory guidelines that differ from other therapeutics. Development depends on individual construction (i.e., attenuated, recombinant, or adjuvant) and purpose – prophylactic or therapeutic. A prophylactic vaccine is directed against a specific infectious disease (e.g., tuberculosis) whereas a therapeutic vaccine is constructed to fight against cancer or an autoimmune disease. Either way, the antigenic properties are specific to the disease. Thus, a robust, efficient safety program design is best determined case-by-case and requires compliance to regulatory requirements, a thorough safety assessment, and appropriate animal model selection.

## Regulatory Guidelines

There are a number of key guidelines, particularly for prophylactic vaccines, including the WHO guidelines, 2005 and 2013; as well as individual health authority guidelines, such as the FDA, for the reproductive and development toxicity, DNA vaccines. In some cases, particularly unique therapeutic vaccines, a specific guideline may not exist. In 2015, Matsumoto et al., (of the Japanese Health Authority PDMA, published a paper presenting the challenges of a therapeutic vaccine and offering guidance in how to address potential on- and off-target toxicities.

## Study Requirements

The safety assessment of a vaccine is critical because prophylactic vaccines – and some therapeutic vaccines – are administered to a healthy population. Designing studies and interpreting subsequent data is of paramount importance. Studies will depend on the vaccine type but must address two pivotal safety aspects: nonclinical toxicology assessment (Module 2 of a CTD[1] dossier), and the product safety characterization (Module 3, quality and CMC) that is required as part of a quality lot release assessment. Choosing a properly equipped laboratory that is both skilled in handling these types of products and has the expertise to interpret the resulting data is key to the overall success of the program.

## Species Selection

Another factor in the success of a vaccine toxicology program is the selection of a single relevant species that accounts for the type of vaccine and related regulatory,

[1]A CTD dossier will be required for all health authority submissions Phase 1 -license

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safety and ethical concerns. The rabbit is often the preferred species, due it ability to generate a humoral immune response. In addition, one can administer the full human dose into a reasonably sized muscle; this supports interpretation of potential local reactogenicity risks. Other species may be used, particularly in cases where the type of vaccine (e.g., an attenuated vaccine) requires a pathogenically sensitive species. Other species include rat, minipig, NHP, or more exotic models like the ferret or guinea pig. In the case of certain therapeutic vaccines, the target homology of the antigen can be an important consideration. Assessing homology and tissue cross-reactivity may be an important starting point. For ethical reasons, the nonhuman primate will be the last species of choice, though it is often the species with the highest homology. A robust vaccine safety program has a dynamic approach and is established on a case-by case basis.

## About the Author

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Dr. Gould is a senior principle scientific advisor with extensive experience (20 + years) in large pharma and biotech, including heading up the nonclinical safety department for Sanofi Pasteur for many years. Sarah has a proven track record in delivering toxicology and safety pharmacology programs, individual studies and regulatory documents (IND, IMPD, CTD) for vaccines/adjuvants, small and large molecules, through the development phases, from Discovery to License. She has supported over 100 submissions and is a contributing author to regulatory guidelines: safety assessment of process residues/contaminants in vaccines (EVM re: TTC, 2012) and WHO vaccine/adjuvant guidelines (2013).