

## Regulatory Considerations in the Safety Assessment of Adjuvants and Adjuvanted Preventive Vaccines

### SLIDE 1

This talk will cover the Regulatory Considerations in the Safety Assessment of Adjuvants and Adjuvanted Vaccines, and focuses primarily on issues associated with adjuvanted preventive vaccines, rather than, for example, therapeutic vaccines.

This presentation reflects the perspective of the Office of Vaccines Research and Review, or OVR, at the FDA Center for Biologics Evaluation and Research, known as CBER, which regulates both preventive and therapeutic vaccines if they are for infectious disease indications. OVR does not regulate therapeutic vaccines for other indications, such as cancer, which are regulated by the FDA CBER Office of Cellular, Tissue and Gene Therapy. These are targeted for a different patient population than most preventive vaccines, so they would likely involve different risk-versus-benefit assessments than those regulated by OVR. Therefore, such vaccines will not be covered in this talk.

### SLIDE 2

Let's begin by reviewing the definition of a vaccine adjuvant and providing a little bit of background. In the Office of Vaccines, an adjuvant is defined as an agent that is added to or used in conjunction with a vaccine antigen to augment or potentiate and possibly target the specific immune response to an antigen. In the U.S., licensed vaccines still contain primarily aluminum-containing compounds as adjuvants. Only one vaccine with a "novel adjuvant" has been licensed, and that is Cervarix, an HPV vaccine that contains AS04 adjuvant. Also, please be aware that in the U.S., vaccine adjuvants are not licensed on their own. Instead, each specific antigen plus adjuvant combination or formulation is licensed. It is possible that this may change in the future, but for now, that is the current approach.

### SLIDE 3

This slide lists some of the possible reasons for including adjuvants in vaccines. Adjuvants can act to improve the immunogenicity of certain types of antigens that are not very immunogenic themselves. They can also enhance the immunogenicity of antigens in certain populations that tend to need immune response enhancement, such as the elderly. In some cases, adjuvants may act to increase the breadth of protection, for example, across multiple strains of influenza or HIV. As a result of all these actions, vaccine adjuvants often have the added value of allowing antigen sparing, which can be very helpful when a large number of doses of vaccine would be needed, as in, for example, an influenza pandemic.

Many adjuvants work by activating both the innate and the adaptive immune systems to induce both humoral and cell-mediated effector mechanisms. This can lead to induction of long-term memory involving B and T cells.

#### SLIDE 4

Adjuvants can be broadly divided into three main types. The first main type consists of those that enhance antigen delivery to antigen-presenting cells and/or the lymph nodes, thereby improving the immune response. Examples are the aluminum salts, the oil and water emulsions, such as Novartis's MF59 and GSK's AS03, and liposomes. The second broad type includes those known as immunostimulators or immunopotentiators. These act primarily by receptor-mediated signaling pathways to modulate the quality of the immune response. Examples are MPL, which activates Toll-like receptor 4, QS21, CpG, cytokines, and others. Finally, the third group consists of combinations of the first two types described, and are known as combinations or "adjuvant systems". GSK has developed several of these. An example is AS04, which consists of MPL absorbed onto aluminum hydroxide. This is the adjuvant that is used in a hepatitis vaccine approved in the European Union called Fendrix, and in the HPV vaccine already mentioned that is approved in the US and known as Cervarix. Other examples of adjuvant systems include the AS02 adjuvant, which consists of MPL and QS21 in GSK's proprietary oil in water emulsion, and AS01 adjuvant, which is MPL plus QS21 in liposomes. These last two adjuvants have been investigated in several malaria vaccine clinical trials.

#### SLIDE 5

The regulatory review process is product-based. Meaning, it is dependent on the characteristics of the specific product. That is why it is often said that CBER approaches issues and questions regarding the information needed to support clinical investigations of adjuvanted vaccines on a case-by-cases basis. Of course, there are some general considerations for designing preclinical studies that support the safety of adjuvanted vaccines, but they should be tailored to the specific product. The clinical trial design is supported by product-specific manufacturing information and available preclinical data. Finally, while the review process is supported by science that is product-based, it is also framed by regulations, as discussed in the next slide.

#### SLIDE 6

Since vaccines are biologics, the regulations for licensure of biologic drug products outlined in Title 21 of the Code of Federal Regulations, or 21 C.F.R., Section 610 are to be followed. The 600s section covers General Biological Product Standards, and has information regarding required testing of products, such as testing for lot release, potency testing, etc.

Adjuvants are covered specifically under 21 C.F.R Section 610.15 for Consistent Materials, which covers not only adjuvants, but other ingredients, such as

preservatives and diluents. There are two main aspects to this regulation that are important. One is that all ingredients shall meet generally accepted standards of purity and quality. This means that either the Investigational New Drug application, called the IND, or the master file would need to include information about the adjuvant as well as the antigen. Such information is usually provided in the form of a Certificate of Analysis that lists results from various lot release tests conducted on the lot of adjuvant to be used in the clinical formulation. Another important aspect of this regulation states that an adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product.

#### SLIDE 7

The next couple of slides describe the Chemistry, Manufacturing, and Controls, or CMC, information regarding the antigen and the adjuvant that should be present in the IND. This should include information about raw materials used, how the antigen and the adjuvant are purified and tested for identity and potency, and whether the adjuvant was tested for pyrogenicity, which only applies to some adjuvants, and for sterility or bioburden. Results from product-specific tests can be included in the submission. For example, if there is a safety concern with a particular class of molecules, a sponsor may be asked to evaluate in animal studies the bioactivity of a particular adjuvant. Finally, like other products, lot release and stability data for the adjuvant should be included in the IND. This would include, for example, information about the degree of absorption and the completeness of adsorption or association for certain adjuvants. It could include data from an assessment of particle size and particle-size distribution and/or stability of emulsion absorption for either the adjuvant itself or when mixed with the antigen.

#### SLIDE 8

Continuing with product characterization information in the IND, it is recommended that sponsors submit information about why they chose the particular antigen and adjuvant combination, and any information from pilot preclinical development studies, where they have determined the rationale for the choice of dose or the ratio of adjuvant to antigen. Also, CBER encourages sponsors to demonstrate not only the immune response to the antigen, but also that the adjuvant enhances this immune response to include, for example, a head-to-head comparison in animals of the immune response to the antigen with and without adjuvant. This is not only helpful for proof-of-concept type of information to demonstrate that the adjuvant works to enhance the immune response, but also for assessing whether the animal species chosen for toxicology studies is sensitive to the adjuvant effect and, therefore, relevant for assessing the safety of the adjuvanted product.

#### SLIDE 9

As previously mentioned, we need to be careful to ensure that adjuvants do not adversely affect the safety of the vaccine. Listed in this slide are the potential

toxicities and safety concerns associated with adjuvants in general. The potential local reactions include, for example, the generation of excessive amounts of proinflammatory cytokines and local inflammation, which can cause severe local reactogenicity, lymphadenopathy and other reactions. In addition, potential systemic reactions can occur, such as the generation of excessive amounts of pyrogenic mediators and the breakdown of self-tolerance. Also, combined toxicities due to interactions between vaccine- and adjuvant-induced mechanisms could lead to severe systemic reactions, potentially including autoimmunity in some individuals. Because of these potential safety concerns, there is heightened sensitivity with regard to conducting toxicology studies with adjuvanted vaccines.

#### SLIDE 10

Thus, an approach is developed toward nonclinical safety testing of adjuvanted vaccines that can aid in supporting entry into clinical trials where human safety is to be evaluated. The hope is that such testing will maximize the benefit-to-risk ratio of vaccine development. Despite the given limitations of animal safety evaluations and their extrapolation to man, such studies may help to provide information on a safe starting dose for clinical studies. In addition, nonclinical testing may aid in the identification and characterization of any unexpected toxicity, and possibly guide the safety monitoring to be carried out when conducting the clinical trial in humans.

#### SLIDE 11

In developing an approach to preclinical safety testing, CBER worked together with other foreign regulators and experts in the field to harmonize expectations. CBER also participated in the drafting of the guidance on nonclinical evaluation of vaccines for the World Health Organization, or WHO. It may be referenced at the website noted on the slide. It is recommended that IND sponsors reference this document for guidance on designing and conducting supportive toxicology studies for new vaccines in general, including adjuvanted vaccines.

#### SLIDE 12

Let's talk about some general aspects of the expected toxicity testing. CBER expects that the toxicity studies be conducted in compliance with Good Laboratory Practice, or GLP. If there are any areas of noncompliance, for example, if some of the immunoassays at times are not GLP compliant, then one would need to identify the areas of noncompliance, as described in the C.F.R. The test articles used in the toxicity studies should be from lots manufactured with the same production process, formulation, and release specifications as lots planned for use in the clinic. Supportive stability data should be developed prior to conducting the toxicology studies, to ensure that the material used in the animal studies is stable. Such stability data should be included in the final toxicology study reports.

#### SLIDE 13

The next four slides will focus on the important considerations for designing adequate toxicology studies for adjuvanted vaccines. For most vaccines sponsors are asked to conduct local tolerance and repeat dose toxicology studies. The dose level and frequency of administration should be similar to that planned for use in the clinic, so at least one full human dose is evaluated. It should not be scaled for body weight or surface area, where feasible. Sufficient time should be allowed between episodic vaccinations, such that an immune response develops and the immune response should be assessed as part of the toxicology study. At least one additional vaccination relative to the number that is planned to be used in the clinical trial should be incorporated into the design of the toxicology study. This is known as the "N plus 1" rule.

#### SLIDE 14

With the repeat dose toxicology study, the product should be administered via the same route of administration that is planned in the clinic. If a delivery device is going to be used in the clinic, it should be used in the animal studies, if possible. Of course you should have appropriate control groups. For example, an inert placebo is often recommended, as well as recovery groups. The sponsor should include a sufficient number of animals per sex, per group, and time point. Usually that is a minimum of three to five of each sex, but for small species, such as mice, more than that is expected.

The recovery group or groups are additional ones that receive the vaccine with the adjuvant, and are allowed to recover 2 to 3 weeks more than the group that you would be sacrificing 1 to 2 days after the last immunization. Otherwise, the recovery group should be monitored and analyzed in the same way as the other groups.

#### SLIDE 15

The next two slides are an overview of the parameters that should be monitored in the animal studies. As part of the "in life" procedures, the animals should be observed clinically on a daily basis. Body weights and feed consumption should be evaluated weekly. Also, body temperature should be evaluated prior to and at 6 and 24 hours after each immunization, and local reactogenicity should be assessed. This should include Draize scoring and assessment of limb use impairment after each injection. Finally, full clinical chemistry, hematology, and immunology assessments should be conducted after the initial vaccination in the series and at the scheduled necropsies.

#### SLIDE 16

As far as the terminal procedures, not only should there be groups that are sacrificed and evaluated 1 to 3 days after the final immunization, but also groups that are sacrificed 2 to 4 weeks after that to allow for recovery as just mentioned. If there is some adverse effect of the vaccine, this will provide an idea of the reversibility of that effect in these animals. Necropsies and analysis of microscopic histopathology should be conducted on sacrificed animals. For most

vaccines, such analyses may only need to be conducted on select tissues, for example, pivotal organs and immune organs. But for a vaccine with a novel adjuvant, we usually ask sponsors to evaluate the full tissue list. The list of tissues provided here is included in the WHO guidance on nonclinical evaluation of vaccines, mentioned previously. Also, biopsies of the injection sites should be taken and assessed histopathologically.

#### SLIDE 17

Now moving on to the timing of the toxicology studies. These should be conducted prior to the submission of the IND. CBER often asks sponsors to submit protocols for their toxicology studies, either as part of the pre-IND package, or in follow-up to a pre-IND meeting for our review and concurrence prior to initiating the studies. When the toxicology study reports are available, they should be included in the new IND or in a master file to be cross referenced to the new IND as mentioned previously. Usually when a pivotal toxicology study is conducted, no additional studies are necessary. If, for example, toxicity was observed during the clinical studies, or if some relevant concerns were reported in the literature, an additional toxicology study may be requested.

#### SLIDE 18

Now a couple of slides about some clinical trial considerations for adjuvanted vaccines in particular. The phase one clinical study should be small, and it can be open label. The population should be appropriate for the clinical trial and inclusion and exclusion criteria should be chosen carefully for phase one studies, to include only healthy adults. Subjects should be closely monitored. Conservative stopping rules for the individuals and the entire study need to be in place.

#### SLIDE 19

For adjuvanted vaccines in particular, it is often asked that at an early stage of development, the added value of the adjuvant in the formulation be demonstrated. Usually the sponsor is asked to come up with a predefined meaningful difference between their adjuvanted and unadjuvanted vaccines for demonstrating the benefit or added value of the adjuvant. The choice of difference would affect the sample size, as would their proposed assay. Also, usually asked early on in clinical development, is that sponsors evaluate the adjuvanted vaccine compared to an inert placebo to obtain preliminary safety information.

#### SLIDE 20

In summary, this presentation covered the regulations for both vaccines in general and adjuvanted vaccines in particular. This talk discussed nonclinical safety assessment of these products, which consists of not only pharmacology and toxicity testing, but also careful biological and chemical characterization of the adjuvant and the antigen. This talk also covered a clinical safety assessment

and the importance of the risk-versus-benefit assessment in the regulatory considerations for adjuvanted vaccines discussed today.

SLIDE 21

On this slide are listed some good review articles that have been published about vaccine adjuvants and adjuvanted vaccines.

SLIDE 22

Listed here are some relevant guidance documents and guidelines.

SLIDE 23

This concludes the presentation, "Regulatory Considerations in the Safety Assessment of Adjuvants and Adjuvanted Preventive Vaccines".

We would like to acknowledge those who contributed to its development. Thank you.