

## Pre-Licensure Review of Preventive Vaccines

### SLIDE 1

This presentation describes the pre-licensure review of preventive vaccines, a process that shares many characteristics of the pre-licensure review for other biological product categories. However, certain attributes are specific to preventive vaccines.

### SLIDE 2

This presentation will cover: an overview of the vaccine development process in general; the pre-clinical evaluation of vaccines; the role of the Investigational New Drug application or "IND" in the approval of biologic products; key attributes in the manufacture and characterization of vaccines and related products; and the clinical evaluation of vaccines. It will conclude by briefly touching on the biologic license application and Phase 4, or post-marketing studies, which follow the pre-licensure process.

### SLIDE 3

This slide broadly shows an outline of the stages in the development of a vaccine, from preclinical development through clinical studies and their alignment with the pre-IND and IND regulatory stages. First, using knowledge of the pathogenesis of a disease target, a sponsor constructs a rationale for a development approach for a vaccine candidate. Next, product components are identified.

For example, a decision may be made to pursue formulating the vaccine antigen with other components, such as adjuvants. The initial manufacturing process is then developed, and preclinical studies are conducted with the vaccine. These steps all represent the pre-IND stage of development. When a sponsor has accrued sufficient data to begin studies in humans, they submit an IND to the FDA. It's possible that additional nonclinical studies will be required if, for example, safety signals are identified during initial clinical studies. During clinical development, sponsors may refine and scale up the manufacturing process. The information associated with these manufacturing changes should be included in the IND.

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Now to pre-clinical considerations.

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The Code of Federal Regulations, or CFR, specifies that adequate information about pharmacological and toxicological studies, either in vivo or in vitro, should be conducted on the basis of which the sponsor has concluded that it is reasonably safe to conduct a proposed clinical investigation.

The regulations also state that the kind, duration, and scope of animal and other tests required will vary with the duration and nature of the clinical investigations. For example, CBER does not always require toxicology studies of preventive vaccines. It is case by case, depending on the type of vaccine.

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The CFR states that each nonclinical laboratory study should be conducted in compliance with the good laboratory practice, or GLP, regulations, or, if the study was not conducted in compliance with those regulations, a brief statement of the reasons for the non-compliance should be provided. The purpose of GLP compliant preclinical safety assessment of vaccines is to generate safety data to support proceeding to Phase 1 studies in humans, to screen for potential toxicities and target organs, to determine a safe dose, and to identify parameters needing additional clinical monitoring in the initial human studies. Ideally, a sponsor should evaluate the antigen/adjuvant formulation that is representative of the clinical lot. However, if that is not possible and the vaccine is used, it should be representative of the clinical lot. For example, the preclinical lot should be manufactured similarly to the clinical lot. The route of administration used in the animal studies should be the same as the route planned in humans. Also, sponsors should evaluate the adjuvant alone in preclinical studies if no data on the adjuvant are available - for example, in a Master file.

A Master File is another type of submission file to which a sponsor, or another manufacturer, can submit information, typically manufacturing information, on a vaccine. That information can be cross-referenced not only by the holder of the master file, but also by other sponsors, with permission of the Master File holder.

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A very important point that CBER frequently emphasizes to sponsors is that they may request a pre-IND meeting in advance of submitting an IND. While a pre-IND meeting is not required, it is highly recommended. CBER frequently tells sponsors that it can only help you to have such a meeting with us. During a pre-IND meeting, CBER can frequently identify potential clinical hold- issues that might otherwise arise during the IND review. A pre-IND meeting can potentially address and resolve these issues, prior to the IND submission. Data submissions can be made to CBER in the pre-IND phase for our review and concurrence. For example, it is in the interest of a smooth IND review to have pre-IND submissions include data to support the clinical studies that will be proposed in the IND; for example, data supporting dose selection for the initial Phase 1 study. Thus, when the IND comes in, it can be reviewed expeditiously, and the proposed clinical study is more likely to proceed in a timely fashion.

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Now let's move on to the IND. In the review of the IND, CBER follows principles as described in the regulations and guidance. Specifically, the CFR states that FDA's primary objectives in reviewing an IND in all phases of the investigation, are to assure the safety and rights of subjects. In Phase 2 and Phase 3 of clinical development, FDA's primary objectives are to help assure that the quality of the scientific evaluation of drugs or biologics is adequate to permit an evaluation of the drug's effectiveness and safety.

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What is the role of the IND in the biologics approval process? It is a mechanism and process to collect clinical data to support the license application, to demonstrate safety and efficacy of the vaccine, and to generate information for the package insert. In addition, chemistry, manufacturing and controls data are generated. These data should demonstrate that the product meets the regulatory requirements of the general biological products standards. Also, the manufacturing process, quality control assays and lot release assays are validated, as are assays that measure the immunogenicity or biological activity of the vaccine. Stability data on the vaccine are also generated during the IND process.

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This slide outlines the overall stages of vaccine oversight from the IND stage to the post-marketing stage. There are three main phases of clinical investigation that take place under an IND: Phase 1, Phase 2 and Phase 3. During all three phases, CBER has constant communication with the sponsors while they do their clinical studies. After Phase 3 testing is complete and, if the data demonstrate the vaccine is safe and effective, the sponsor may then submit an application for licensure. This is called a Biologics License Application, or B.L.A.

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Let's go into more detail about the IND phase and the information that is included in the initial IND submission for CBER review. As noted earlier, the IND includes information about the manufacturing process, vaccine characterization, and preclinical testing, such as toxicity in animals. Definitive toxicology testing should be conducted according to Good Laboratory Practice, or GLP. If not, there should be an explanation. This point will be elaborated later.

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Now, let's discuss the manufacturing and characterization of vaccines.

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There are some common principles for vaccine production and quality control. A sponsor should have manufacturing procedures that ensure consistency of production. The product components should be defined and compatible, and the

vaccine should be well characterized. This characterization should include the development of specifications to ensure consistency of manufacture. Depending on the product, testing for adventitious agents may be required. All products should be free of extraneous materials. In addition, stability data for the vaccine should be generated.

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In 2008, FDA published a Final Rule and guidance document, which addressed current Good Manufacturing Practices, or cGMPs, for Phase 1 investigational products. CBER understands that early on, a sponsor is not going to have all product assays validated by the time of licensure. That is not expected. But as the sponsor goes through clinical development, assays should be more finely tuned, and eventually validated. The same is true of the processes used to manufacture the vaccine. Some aspects of manufacturing, testing for sterility for example, will be required during all phases of clinical investigation and after licensure. However, the extent of manufacturing controls needed to achieve appropriate product quality will differ between investigational and commercial manufacture, as well as during the various phases of clinical development. Thus, CBER accepts an incremental approach to meeting full cGMPs.

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Let's briefly discuss the importance of assays in vaccine development. Assays are used to detect vaccine-elicited immune responses. These responses may be important for an assessment of efficacy, for example, as a component of a case definition. In addition, assessment of immunogenicity is one measure of consistency of manufacture. But there are some challenges to the development of assays. For example, considerable research and development may be necessary. Also, depending on the product, functional antibody assays may be needed in addition to those in which one just looks at antibody binding.

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Biologic products, as a class of products, require lot release testing, a subject more broadly addressed in another presentation and will not be covered in detail in this presentation.

However, some specifics in the area of vaccine licensure may be helpful in this current discussion of manufacturing and quality controls. What kind of lot release testing does FDA expect for vaccines? It would include testing for sterility, for general safety to detect extraneous toxic contaminants, and for identity, purity and potency. Potency testing could involve in vivo or in vitro tests, or both. In addition, tests should be developed to demonstrate removal of process contaminants.

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Let's move on to clinical testing of preventive vaccines under IND.

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The first stage of clinical investigation of a new vaccine is called Phase 1. The primary objectives and endpoints during initial Phase 1 clinical studies of a vaccine are related to safety and tolerability. There are a limited number of subjects in these studies, usually 20 to 80, and typically, these are healthy adults 18 to 50 years of age. Subjects are closely monitored for safety in Phase 1 studies.

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During phase 1 studies, subjects are closely monitored for local and systemic events. The goal of this is to ensure that any adverse outcome is captured, and that subjects are not exposed to unreasonable risk. Subjects have to visit the clinic for an initial clinical exam. In many studies, subjects are provided a diary card on which to record adverse events. At subsequent clinic visits, the cards are reviewed and follow-up clinical exams can be conducted. In many studies, the clinic visits can include blood draws for hematology and clinical chemistry laboratory studies. It is very important, especially in these early phase studies, to have "stopping rules". These spell out the specific adverse event criteria which, if met, will result in a pause, or halt, to the study or the immunizations. During such a pause, the specific adverse event will be investigated before deciding whether to proceed further with vaccinations, or stop the study entirely.

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Now let's discuss Phase 2 clinical studies. The primary objectives for a Phase 2 study of a vaccine are related to safety and immunogenicity. However, these studies typically include up to several hundred subjects per trial. The studies are often randomized and controlled. In certain situations, they may include subjects at high risk for the infectious disease of interest. These Phase 2 studies are typically used to identify the preferred dose, immunization schedule, vaccine formulation and route of administration before advancing to pivotal Phase 3 studies.

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During Phase 2 clinical trials, one can get more precise estimates of common adverse events, such as local reactogenicity, and systemic effects. The immune response elicited by the vaccine is assessed, and this assessment may be quantitative and qualitative. Sometimes, there is a pilot evaluation of the proposed efficacy endpoints. Some studies are designed to include an evaluation of immune interference with other concurrently administered vaccines.

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Let's move now to the Phase 3 studies of preventive vaccines. Phase 3 pivotal studies include an assessment of product efficacy. The specific endpoint for this objective will be product dependent. For example, it may be feasible to conduct a clinical disease endpoint efficacy study. In some cases, for example, if the disease incidence is too low, or there is a well accepted correlate of protection, it

may be appropriate to use an immune response endpoint. In certain specific situations when it is not ethical or feasible to conduct an efficacy study in humans, the pivotal efficacy of the product may be demonstrated in animals. This is termed the "Animal Rule" approach. Products approved under the "Animal Rule" would still need adequate safety data from human studies. Regardless of path to licensure, the pre-licensure safety database will include thousands of subjects.

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Phase 3 efficacy studies are typically double-blinded, randomized and controlled. In the case of clinical disease endpoint, knowledge of the background epidemiology is essential for sample size and power calculations. As far as case definitions are concerned, they should be well defined using clinical criteria and validated assays for laboratory diagnosis, such as culture and serology. The case definitions that are chosen should have clinical relevance. Phase 3 pivotal studies can include several thousand subjects. Although the primary objective is efficacy, safety and immunogenicity of the vaccine will also be evaluated.

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Safety is defined in the CFR. It is the relative freedom from harmful effects to persons affected directly or indirectly by a product, when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

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Typical safety endpoints included in Phase 3 studies include death, nonfatal serious events, or SAEs, non-serious unsolicited adverse events, and solicited local adverse events, if the vaccine is administered by subcutaneous or intramuscular route. There will also be an assessment of solicited general adverse events; for example, fever, loss of appetite and headaches.

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Upon completion of Phase 3 pivotal studies, the sponsor will submit a report and the FDA IND team reviews the data. Typically, there will also be a formal meeting or communication with the sponsor. If the data are favorable, the manufacturer may decide to submit a Biologics License Application, or BLA, to CBER. The BLA is a marketing application. The purpose of a BLA is to provide adequate information to allow FDA reviewers to reach a decision that the biological product is safe and effective for its proposed use, and that the proposed benefits outweigh the risks. The information included in the BLA will determine FDA's assessment of the adequacy of the proposed labeling, and the adequacy of the manufacturing and control methods

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If a BLA is in fact submitted, a committee will be constituted to review the application. Following review, a decision will be made to approve the application

or not. This decision will be based not only on the information included in the application, but also on an evaluation of the manufacturing facility and process during a "pre-license inspection."

In addition, FDA and the manufacturer may take the application to an advisory committee of outside experts for input. Assuming the license is granted, further studies, sometimes called Phase 4 studies, can be requested as post-marketing commitments. There will also be facility inspections conducted after licensure. Manufacturers frequently update their licenses with new information, such as clinical data to support new indications or populations for use of the product, as well as additional updated manufacturing information. These requests to update their license are called "supplements."

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After licensure, post-marketing studies of the vaccine are frequently conducted. These generate additional information about the safety, efficacy or optimal use of the vaccine. These studies are either required of, or agreed to, by the sponsor. These commitments are described in the approval letter and are posted on FDA's website.

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To conclude, you've seen that preventive vaccines have unique considerations for product and clinical development. Product characterization and manufacturing information is reviewed by the FDA. Assays are developed and validated. Nonclinical safety assessments are a key component in vaccine development. Accumulation of safety, immunogenicity and efficacy data are done during development, and reviewed by CBER. This review and regulation helps facilitate development of safe, pure and potent new vaccines that are manufactured consistently and according to current good manufacturing practices.

#### Slide 30

This concludes the presentation, "Pre-Licensure Review of Preventive Vaccines".

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