Regulatory Perspective on Development of Preventive Vaccines for Global Infectious Diseases

SLIDE 1

This presentation presents regulatory perspectives on the development of preventive vaccines for global infectious diseases. FDA has posted a guidance document, "Guidance for Industry: General Principles for Development of Vaccines to Protect Against Global Infectious Diseases" that provides current FDA thinking in more detail.

FDA developed this guidance document to answer questions and concerns regarding:

ONE: Whether FDA can license vaccines to protect against infectious diseases or conditions that are not endemic or have not been reported to occur in the US;

TWO: Whether the regulatory pathways to US licensure for the development of vaccines to protect against infectious diseases that are not endemic or have not been reported to occur in the US are the same as for vaccines to protect against diseases that are endemic in the US; and

THREE: Whether Sponsors may submit data from clinical trials conducted outside the US to support product licensure.

SLIDE 2

This presentation addresses:

The public health need for vaccines against global infectious diseases, the applicable legislation and regulations that govern development of vaccines, FDA licensure pathways for vaccines, considerations concerning the conduct of foreign clinical trials, and FDA approaches for expediting vaccines for serious illnesses and conditions.

SLIDE 3

In the last decade, we have witnessed the increased prevalence of emerging and re-emerging infectious diseases that threaten global public health. These include Dengue, tuberculosis, malaria, enteric diseases, Zika, Influenza Viruses H1N1 and H7N9, Ebola, MERS, and other threats.

Safe and effective vaccines are needed against these and future threats.

Development and increased availability of vaccines against global infectious diseases will benefit US and global public health.

SLIDE 4

Can the FDA license vaccines to protect against infectious diseases or conditions that are not endemic or have not been reported to occur in the US? Yes. Legislation and regulations that permit FDA to license vaccines against certain global infectious

diseases are reviewed on the next slide.

SLIDE 5

FDA's authority to regulate drugs and biologics, including vaccines, rests in Section 351 of the US Public Health Service Act. The Food and Drug Administration Act of 2007 amended the Food Drug and Cosmetics Act to allow FDA to grant priority review for treatment and prevention of specified tropical diseases, including tuberculosis, malaria, cholera, and "any other infectious disease for which there is no significant market in developed nations."

Specific regulations found in the Code of Federal Regulations, or CFR, apply to the evaluation of investigational vaccines and provides pathways to marketing approval or licensure of these products.

SLIDE 6

Clinical studies supporting the licensure of biologics in the US are required to be conducted under an Investigational New Drug application, known as an "IND."

This slide outlines the stages of vaccine review and regulation using the US IND process -- Phase 1 through post-approval Phase 4.

Under FDA regulations, vaccine and related products are progressively evaluated in clinical studies to establish safety, immunogenicity, and effectiveness. Permission to conduct clinical studies occurs only after FDA review of an IND application. Clinical studies may become more complex and larger in size as products move through the different phases shown. Phase 1, 2 and 3 clinical studies may culminate in submission of a complete Biological License Application, known as a BLA, that provides FDA with all the information and data required for review and possible licensure. Studies may also be conducted post licensure in Phase 4 to provide additional safety and effectiveness data, if needed.

There is also the opportunity for Sponsors to request a pre-IND meeting. In the pre-IND meeting, FDA may review and discuss with the sponsor their pre-clinical studies, address any pharmacology toxicology questions, and review the proposed clinical development plan for the product. Additional information is provided in the FDA "Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products."

Most vaccines are first studied in healthy adults, to obtain initial information concerning the safety and the immunogenicity of a product. Then, as more information is known, the study proceeds into the population of interest. Before studying the product in children, information is needed regarding the prospect of benefit and whether it may be efficacious.

SLIDE 7
Can Sponsors submit data from clinical trials conducted outside the US to support product licensure?

Yes. Under 21 CFR 312.120, FDA will accept as support for an IND or to support an application for marketing approval a well-designed and well-conducted foreign clinical study not conducted under an IND if certain conditions are met.

SLIDE 8
FDA accepts the data from foreign clinical trials not conducted under IND provided the studies are relevant, well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be used to support clinical investigations in the US and/or licensure. The regulations that specify these conditions in more details are contained in 21 CFR 312.120.

SLIDE 9
Clinical studies done overseas, may or may not be conducted under US IND.

The advantages of conducting these overseas studies under the US IND process include allowing for prospective dialogue regarding acceptable clinical trial design, and outlining potential issues. In formal pre-submission meetings, FDA has a chance to preview the Sponsor's plans regarding clinical, product, and chemical data, their phase three study plans, their proposed basis for licensure, even their electronic format for submission. This is an opportunity to provide regulatory guidance, as FDA is involved in discussions with members of the World Health Organization, known as WHO, with industry, and with academic centers regarding clinical development and licensure of products, such as malaria, HIV vaccines, and tuberculosis vaccines.

If the sponsor elects to do overseas studies not conducted under US IND, referred to here as the "non-IND studies", there is a risk that it may be found later that the studies do not satisfy US regulatory requirements. FDA may require additional clinical studies, which may delay the filing of their biologics license application, or BLA. There is the potential that FDA and the sponsor may have different viewpoints concerning the sponsor's chosen efficacy endpoints. Or, the safety evaluation and methodology may not be considered acceptable due to issues regarding the choice of time-points for surveillance or types of pre-specified adverse events that were monitored.

SLIDE 10
What is the regulatory path forward to US licensure of a vaccine to protect against an infectious disease that is not endemic or has not been reported to occur in the US?

Sponsors will use the same path for vaccines against infectious diseases endemic in the US.

SLIDE 11
Only those vaccines that are demonstrated to be safe and effective and can be manufactured in a consistent manner will be licensed by the FDA.

For the FDA, "effectiveness" means that all indications, for example prevention of disease, must be supported by substantial evidence of effectiveness."

Demonstration of effectiveness is based on adequate and well-controlled clinical studies using a product that is standardized as to identity, strength, quality, purity and dosage form.

SLIDE 12
"Safety" means the relative freedom from harmful effects. As such, the Sponsor must submit a safety database to the FDA for review. Some considerations that influence the size and parameters of the safety database include: the characteristics of the vaccine product, possible safety signals or theoretical safety concerns, the target population, the intended use of the product, and the seriousness of the disease targeted for prevention. When considering the approval of a product, FDA carefully evaluates the risks and benefits of using a product.

SLIDE 13
There are three pathways for the licensure of vaccines: Traditional Approval, Accelerated Approval and "Animal Rule" approval.

We'll be discussing each of these paths in turn. In each case, demonstration of clinical safety is required. Demonstration of effectiveness is also required for all pathways; however, there are differences in approach among the pathways.

Accelerated Approval and "Animal Rule" approval have specific "eligibility" criteria and requirements.

SLIDE 14
Traditional Approval is based on adequate and well-controlled clinical studies demonstrating prevention of disease or a response to a scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay. Approval is facilitated by an understanding of disease pathogenesis and the mechanism by which a vaccine prevents disease.

SLIDE 15
Clinical trials demonstrating preventive efficacy using clinical endpoints provide the greatest scientific rigor in evaluating vaccines. These studies are prospective, controlled, and randomized. The primary endpoint is the prevention of disease.

Clinical endpoint efficacy studies are usually necessary in situations where the vaccine is novel, the first of its kind administered to a target population, and when there is no accepted immune response or correlate of protection.

Prevnar, a heptavalent conjugate pneumococcal vaccine, is an example of a product that was licensed using a clinical efficacy endpoint. In the Northern California Kaiser Permanente trial, Prevnar was studied in 38,000 infants for the prevention of invasive pneumococcal disease.

FDA has posted its advice concerning assessments of efficacy in "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products."

SLIDE 16

Two efficacy trials are usually the standard, but one trial can be adequate if the results are compelling. This is often the case for the vaccine efficacy trials. Some of the multicenter vaccine efficacy trials have enrolled 30,000 to 70,000 subjects.

SLIDE 17

Sponsors may wish to pool results from different clinical studies. To adequately support efficacy, statistical criteria should be prospectively defined in the Statistical Analysis Plan, or SAP. There should be similarities in primary outcomes, in adverse event definitions, in eligibility criteria, in the dose and dosing regimen and the types of concomitant vaccines that are administered, which can be a big issue with children, in baseline status and health of the study population, in the duration of follow-up for adverse event and safety monitoring, in the medical practice in the community, in the availability of Emergency Room treatment, and in management and documentation of withdrawals and dropouts.

SLIDE 18

Results from the studies to be pooled should be in general agreement. Studies to be pooled should not contradict each other. Any variation in study design and conduct might introduce bias or imprecision in the individual estimates of treatment effect. Generally, the background incidence rates of a disease should be similar, to avoid differences in the variance estimations.

SLIDE 19

A Correlate of Protection is a laboratory parameter that has been shown to be associated with protection from clinical disease. For vaccines, this is often a scientifically established immune marker. In order to be useful for demonstrating effectiveness, a Correlate of Protection is most useful if qualitative and quantitative relationships can be determined.

SLIDE 20

Examples of licensed vaccines with an identified correlate of protection include Hemophilus influenza type B and Hepatitis B vaccines. Identification of a correlate of protection, however, is not a requirement for licensure. Examples of licensed vaccines without an identified immune Correlate of Protection include the acellular pertussis vaccine, typhoid vaccine, and BCG vaccine for tuberculosis. If there is an immune

response that correlates with protection, it's useful for interpreting trials with immune response endpoints. It also allows for bridging across populations. An immune response endpoint can be helpful if you want to bridge from an older population to a younger one.

SLIDE 21

For products addressing serious or life-threatening illnesses and provide meaningful therapeutic benefit, FDA can grant Accelerated Approval based on a determination that the effect of the surrogate endpoint is reasonably likely to predict clinical benefit. Clinical benefit must be verified post-licensure.

SLIDE 22

A surrogate endpoint is defined as a laboratory or physical sign that is used in a therapeutic trial as a substitute for a clinically meaningful endpoint. It's a direct measure of how a patient feels, functions, and survives. It is expected to predict clinical benefit. Influenza virus vaccines have been approved by using surrogate immune markers and the Accelerated Approval pathway. In those cases, an immune response tighter of greater than or equal to 1 to 40 to hemagglutinin, and a fourfold rate of seroconversion are used as surrogate markers of clinical benefit.

FDA also may consider an Intermediate endpoint, which is defined as measures of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality, or IMM.

SLIDE 23

The "Animal Rule" provides a third way to support a claim of efficacy. If human efficacy studies are not ethical or practical, the FDA may accept data from appropriate animal models as evidence of effectiveness. This would apply to new drugs or biologics that are intended to treat or prevent life-threatening or serious conditions such as smallpox. While efficacy would be based on adequate and well-controlled animal studies, safety still must be demonstrated in clinical trials. The Sponsor must verify clinical benefit post licensure if the opportunity arises. The Animal Rule does not apply if one of the other licensing pathways is possible. FDA's regulations concerning the approval of new drugs when human efficacy studies are not ethical and field trials are not feasible are codified in 21 CFR 601.90 through 601.95 for biological products.

SLIDE 24

The animal study endpoint chosen should be clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allow for the selection of an effective dose in humans.

SLIDE 25

All studies subject to the Animal Rule must be conducted in accordance with pre-existing requirements under the Good Laboratory Practices, or GLP, found in 21 CFR 58 and the Animal Welfare Act, codified at 7 USC Section 2131. GLP will be required for the definitive/pivotal animal studies or studies that provide data for the label. Exploratory studies may not be conducted under GLP.

SLIDE 26

Prior to conducting any clinical studies, Sponsors may benefit from consultations with FDA early in vaccine development. Some considerations include a description of the disease to be prevented or treated, the criteria for subject selection, the choice of the control group, and the key clinical trial design parameters, such as efficacy and safety endpoints, dose and dosing, the study duration, the concomitant medications, and vaccines to be used. For most vaccine clinical studies, FDA requests that subjects be followed for at least 6 months after the last vaccine dose is administered. Safety assessment and the methodology to be used is looked at. FDA needs to understand the standard of medical care and practice in the community where the clinical trial is going to be conducted. FDA also looks to see if the study will provide clinical data in relevant demographic groups that are often underrepresented in US clinical trials. Discussions with the Sponsor clarify whether the studies being conducted overseas will be conducted under US IND or not. FDA wants the Sponsor to outline the study rationale. Any overseas clinical studies should comply with the Code of Federal Regulations, which outlines the requirements for foreign studies that are not conducted under US IND.

SLIDE 27

All underlying ethical principles must be met for clinical studies to be accepted by the FDA. Studies must meet local and international standards; and Good Clinical Practice, or GCP standards should be followed. GCP standards may be found in the International Council for Harmonisation, or ICH guidance "E6: Good Clinical Practices". Other requirements include adequate safety monitoring, informed consent and a complete investigator brochure are necessary. Additional regulatory requirements are posted on: www.fda.gov. Follow the link shown on this slide.

SLIDE 28

There are regulations regarding the protection of human subjects in the Code of Federal Regulations, shown here. It is essential that no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Additional directions are contained in the regulation, including safeguards for children in clinical investigations.

SLIDE 29

Safety monitoring protects subjects by monitoring local, systemic, and potential end-organ toxicity, looking to identify any major toxicity. With clinic visits, it is expected that the subjects' symptoms will be reviewed. The clinical trial subjects may use

diary cards where they keep a record of temperature and symptoms for 7 to 14 days after vaccination. Clinic visits may include a clinical exam and vital signs. Laboratory studies can include hematologic studies, chemistries, and looking at hepatic, renal, urinalysis and endocrine outcomes. The type of safety monitoring done will depend on the product. Often the preclinical product evaluation may inform what types of tests are going to be used to monitor safety when the product goes into Phase 1, Phase 2, and Phase 3 clinical trials.

SLIDE 30

The protocol should include the safety parameters to be evaluated and the time schedule for assessment. Active post-vaccination monitoring does not stop at 30 days after vaccination. With use of new adjuvants in vaccines, there is interest to see if there are any autoimmune diseases that may develop at a later time post-vaccination. Provision for longer term follow-up beyond 6 months should be outlined. Safety monitoring tools should be submitted to the IND with the protocol, including the case report forms and the diary cards. For vaccines going into a healthy population, FDA recommends that the Sponsor use the toxicity grading scale designated for normal healthy adults. FDA found that sponsors were using toxicity grading scales that had been used in HIV and cancer trials. So, FDA recommended that more conservative toxicity grading scales be used and devised a toxicity grading scale for healthy adults that was more appropriate. You can see the web link listed for more information.

Scripted interviews should be considered during safety follow up. Structured interviews can be very helpful if you have particular safety issues for investigators to pursue. For example, investigators worried about cardiac symptoms after a particular vaccine, can use a structured interview which asks about chest pain and shortness of breath. Photos of vaccination sites may be helpful for evaluating local reactogenicity.

SLIDE 31

Toxicity grading scales have been discussed.

A data safety monitoring board in Phase 1 is not required except for clinical studies in children.

Stopping rules are used in early phase studies, such as phase one and phase two. Stopping rules can be very helpful, and they are devised so if a certain number of subjects have a grade three or a grade four type of adverse event, then the study will temporarily pause. In early phase studies, FDA tends
to ask for reporting of adverse events regardless of whether or not the sponsor is convinced that the adverse event is caused by the study product or not.

SLIDE 32

Considerations for foreign clinical trials include being cognizant of efficacy and immunogenicity differences in populations and making sure that all of the clinical

data are collected appropriately, with use of appropriate case definitions and sample size. Sponsors should be aware of differences in the schedule of immunizations as compared to US recommendations.

SLIDE 33
ICH has published the document "E5: Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data." This guidance provides the framework for evaluating the impact of ethnic factors on a drug's effect. The document also provides regulatory and development strategies to permit adequate evaluation of the influence of ethnic factors, to minimize duplication of clinical studies and to expedite the drug approval process.

SLIDE 34
Bridging studies are supplemental studies performed in a new region which will provide clinical data to bridge to a particular population. You can do bridging studies for efficacy based on immune response criteria and for safety in a new population.

SLIDE 35
Some types of bridging studies that may need to be done include those to address a new population, different age group, new product for standard of care, new schedule, and manufacturing changes. If the immune response and safety profile are similar, then efficacy can be inferred.

SLIDE 36
Clinical endpoint efficacy trials may not be possible in some regions. It is still possible to bridge to the US population. The disease target may be endemic in limited or dangerous geographical areas. In other cases, existing vaccines may be available that that would limit the study population or interfere with study results. One approach to overcome these obstacles is to conduct clinical efficacy trials where disease rate is high, then "bridge" to the US population with a single-arm study in the US.

SLIDE 37
It may not be possible to randomize a region or ethnic group but the study can still be adequately controlled.

Bridging studies should keep the comparison groups similar with regard to group demographics, medical practice and conduct of the trial.

SLIDE 38
This slide presents some additional issues that should be considered when conducting clinical studies.

SLIDE 39
Early consultations are recommended so FDA can address issues with co-administered vaccines. Among FDA's concerns are

1) the pivotal data with use of US co-administered vaccines on a US-schedule, meaning data only from non-US countries or pooling US and non-US data, and sub-analysis by country;

2) the pivotal data with co-administered vaccine licensed in non-US countries that the sponsor believes are the same as US-licensed vaccines, for example Prevnar in the US vs. Prevenar which may be used external to the US; and

(3) pivotal or supportive data with "US-like" co-administered vaccines, that is, combination vaccines containing antigens also included in US licensed vaccines.

SLIDE 40

For human challenge studies, complete chemistry, manufacturing and controls, called CMC, information is needed on the challenge organisms to be used. The challenge model should be developed under IND to ensure that it will be an appropriate indicator for assessment of vaccine activity.

Human challenge studies have been a critical component of "proof of concept" studies for malaria for over 40 years.

In 1993 and 1998, the FDA convened the Vaccines and Related Biologics Products Advisory Committee meetings to consider whether data from human challenge studies in US subjects could be sufficient to demonstrate efficacy of a cholera vaccine in travelers to endemic areas, or to residents in cholera affected areas, who are at high risk for contracting the disease. The committee agreed that human challenge studies could suffice to demonstrate efficacy of a cholera vaccine provided that studies were adequate, well controlled, and conducted under the provisions of GCP. Of note, use of challenge studies to demonstrate effectiveness may not preclude the requirement for large Phase 3 safety studies.

SLIDE 41

Early on in clinical development of a novel adjuvanted preventive vaccine, a comparative study of adjuvanted versus non-adjuvanted vaccines should be conducted to demonstrate that the immune response elicited by the adjuvanted antigen is significantly better than that elicited by the same antigen alone. For sample size determination, the sponsor should pre-define what would constitute a meaningful difference. One statistical approach to addressing the added value of a vaccine adjuvant is described in two FDA guidance documents, for example, "Guidances for Industry on Clinical Data Needed to Support the Licensure of Influenza – Trivalent and Pandemic - Vaccines."

In addition, although a placebo group is not required in a Phase 1 clinical study of an adjuvanted vaccine, inclusion of a placebo group may enhance interpretation of the initial safety data. The use of a saline placebo is preferred over an adjuvant alone arm, if there will be only one control group. In advanced development of an adjuvanted vaccine, for example, for a Phase 3 efficacy trial, which will often provide

the definitive safety data for the new vaccine, a saline placebo is strongly preferred to permit the clearest interpretation of safety for the product to be proposed for licensure.

SLIDE 42

The Pediatric Research Equity Act of 2003, or PREA, addresses product development for pediatric uses. Pediatric assessments are to be included in all applications submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, unless the sponsor has obtained a waiver or deferral from FDA. Pediatric assessments may be obtained from clinical bridging studies in order to permit extrapolation of efficacy to a pediatric population. In addition, adult efficacy data can be extrapolated to the pediatric population when it is likely that the disease and response to treatment in adults and children are reasonably similar.

SLIDE 43

This slide has additional information on pediatric vaccine development and PREA. ICH E11 provides regulatory guidance regarding pediatric research.
21 CFR 50 directs IRBs regarding allowable research in children.
PREA requires assessments of drugs/biologics including vaccines in all relevant pediatric populations.

SLIDE 44

There are mechanisms in place to facilitate product development for vaccines with high public health impact. We previously discussed the aspects of Accelerated Approval. Additional mechanisms include Fast Track,
Breakthrough Therapy Designation, and Priority Review.

SLIDE 45

Fast track programs are designed to facilitate the development and expedite the review of drugs that are intended to treat serious or life-threatening conditions, and what is called an unmet medical need, where there is no particular product for the relevant type of cancer or infection. The Fast Track program was authorized in the Food and Drug Modernization Act. The designation applies to the combination of the product, and a specific indication that is being studied.

SLIDE 46

Fast track adds to existing programs. The bottom line is it allows for a rolling submission of data and a lot more contact with the FDA. There is a lot of communication in end of phase one meetings and other meetings. End of Phase 2, and pre-BLA meetings are strongly recommended. It's all designed to expeditiously get these very important products to market.

SLIDE 47

Products are eligible for Breakthrough Therapy if the preliminary clinical evidence in effectiveness or safety may demonstrate substantial improvement over available therapies for a serious condition on one or more clinically significant endpoints.

The Breakthrough Therapy designation provides the Sponsor with intensive guidance on efficient development of their product and a commitment from the FDA to work together to expedite the development. Sponsors are also permitted to submit via the same rolling review process as the fast track designation.

If the designation is no longer supported by subsequent data, FDA may rescind the designation.

SLIDE 48

Products that are regulated by FDA are eligible for Priority Review if they provide a significant improvement compared to already marketed products. This is a six month review of the entire BLA rather than the usual 10-month review. Products that come in for fast track are later evaluated to see whether FDA is also going to give it a priority review. Cholera Vaccine is an example of a product that was approved by using priority review.

SLIDE 49

Will FDA grant priority review to a BLA submitted for a vaccine indicated for a disease not endemic to the US? Yes, if appropriate criteria are met. Vaccines to prevent diseases such as malaria, tuberculosis, and HIV would be considered very important products.

SLIDE 50

FDA is committed to assist in the development of vaccines to prevent global infectious diseases even if the US market may be limited and the primary target populations are in developing countries. The US regulatory process and licensure approval process can support the development of vaccines to protect global public health.

SLIDE 51

This concludes the presentation, "Regulatory Perspective on Development of Preventive Vaccines for Global Infectious Diseases." We would like to acknowledge those who contributed to its development. Thank you.