Regulatory Perspective on Development of Preventive Vaccines for Global Infectious Diseases

SLIDE 1

This talk will provide some regulatory perspective on the development of preventive vaccines for global infectious diseases. CBER has posted a guidance document regarding this subject.

CBER developed this guidance document in an attempt to answer questions and concerns regarding:

Whether FDA would license vaccines for infectious diseases endemic overseas which may not occur with any high prevalence in the US;

Whether FDA would accept clinical trial data to support vaccine licensure from studies that are mainly conducted overseas; or

Whether the process and pathways to license vaccines to prevent tropical diseases would be the same regulatory pathways used to license other vaccines.

SLIDE 2

This talk:

Addresses the impact of global infectious diseases;

Discusses vaccine development using our investigational new drug process, called IND;

Covers how FDA can accept clinical data from trials that were conducted overseas and not necessarily conducted under US IND, as was done for the licensure of the GSK rotavirus vaccine, ROTARIX. The ROTARIX clinical studies were mainly conducted overseas, except for a group of infants that were studied under IND in the United States. It was necessary to have this data, in order to be sure that ROTARIX did not interfere with the immune responses to other US licensed childhood vaccines that infants would receive according to the US schedule for childhood immunizations.

This talk will review the regulatory frameworks and standards used in clinical development, including ethics, good clinical practice, and study conduct issues.

And, it will touch on the applicable regulations; as well as review novel mechanisms and pathways for approval that have been used to license new vaccines.

SLIDE 3
Some reasons regarding the need for expedited pathways for these vaccines to prevent infectious diseases are outlined on this slide.

Global climate changes may impact certain vectors, animal populations, tick and flea populations, and prevalence of disease may consequently change.

Throughout the world, natural and manmade disasters occur, and raise new health concerns for refugees and immigrants.

We have specific vaccine needs for military who are deployed and also for travelers.

Pandemic strains of influenza have circulated.

The threat still exists that a bioterrorism agent such as smallpox or anthrax could be used.

And, vaccine shortages may occur.

SLIDE 4
There are limitations and challenges if vaccine studies were only allowed to be conducted in the U.S.

Epidemiology could limit the ability to conduct efficacy studies, because there might not be a particular infectious disease in great prevalence here in the U.S.

Interest in enrollment in vaccine studies could be limited for a product to prevent a viral infectious disease for which there is already a US licensed antiviral drug. Thus, there may be more interest in clinical trial participation for such a product overseas where the infectious disease may be more prevalent and access to antiviral drugs may be more limited.

Sponsors would prefer to submit one application to US and other regulatory authorities.

If FDA only accepted US data to support US licensure, then this could delay introduction of medically important products for the US population.

SLIDE 5
Clinical studies in the US are required to be conducted under US IND. Clinical studies done overseas, may or may not be conducted under US IND.

Advantages of conducting these overseas studies under U.S. 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 TB vaccines.

If the sponsor elects to do overseas studies not conducted under US IND, referred to here as the "non-IND studies", then there is a risk that it may be found later that the studies do not satisfy U.S. regulatory requirements. FDA may require additional clinical studies, which may delay the filing of their biologics license application, or BLA. There could be potential for differing views between the sponsor and CBER regarding efficacy endpoints that the sponsor has chosen. 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 6

All underlying ethical principles have to be met. Research has to meet local and international standards. And, good clinical practice standards should be followed. Adequate safety monitoring, informed consent and an honest investigator brochure are necessary. Additional details are outlined in the Code of Federal Regulations.

SLIDE 7

When discussing study conduct with Sponsors, it is helpful for them to describe 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 U.S. clinical trials. Discussions with the Sponsor ask 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 8

What is the regulatory path to U.S. licensure for a vaccine that is targeted for a disease or conditions that are not endemic in the U.S.?

It is the same regulatory pathway as that used for a product to prevent a disease that is present here in the U.S. There is no difference.

SLIDE 9

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

There is also the opportunity for a pre-IND meeting. Sponsors who utilize this pre-IND meeting find it helpful. In the pre-IND meeting, FDA has discussed with the sponsor their pre-clinical studies, and addressed many of their pharmacology toxicology questions. Thus, when they submit their new IND, they are more prepared.

Most of the vaccines are first studied in healthy adults, to get an idea regarding the safety and the immunogenicity. 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 10

Does CBER use a different standard for evaluating vaccine products that are meant solely for the foreign market versus the U.S. market? No. The same standards apply, and CBER will review some of the aspects of the efficacy and safety evaluation for vaccines.

SLIDE 11

For vaccine efficacy, there are three main approaches for showing that a vaccine works.

A clinical endpoint can be used to demonstrate efficacy. For instance, with the rotavirus vaccines, there was no immune response that predicted protection against rotavirus disease. There was no correlate of protection. Instead, a clinical disease endpoint was used, which requires that you have a case definition for what is rotavirus disease.

In other trials, it may be possible to use an immune response parameter that correlates with protection. An example of this would be the Haemophilus or the hepatitis B vaccines.

Finally, ways to demonstrate efficacy would be using the Animal Rule, which will be discussed a bit later. An example would be some of the smallpox vaccines in

development. Immune assessments are still critical for clinical endpoints, even if the animal rule is used.

SLIDE 12

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, such as with the hepatitis B vaccine.

An example of a vaccine that utilized a clinical efficacy endpoint would be the Northern California Kaiser Permanente trial evaluating Prevnar, the heptavalent conjugate pneumococcal vaccine that was studied in 38,000 infants.

SLIDE 13

In the assessment of efficacy, FDA has a May 1998 Guidance for Industry that provides clinical evidence of effectiveness for human drugs and biological products. 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 14

Let's briefly touch on statistical considerations for pooling clinical trial data, because sometimes Sponsors come in and they want to pool results from different clinical studies. If people are going to pool study data to support efficacy, it should be prospectively defined in the statistical analysis plan. 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. Results from the studies, if you are going to pool, should be in general agreement, because you don't want contradicting studies, and any variation in study design and conduct that might introduce bias or imprecision in the individual estimates of treatment effect. You also don't want to have major differences in background incidence rates of a disease that could cause differences in variance estimations.

SLIDE 15

The correlate of protection is the Holy Grail in vaccine development. Generally, it's a laboratory parameter that has been shown to be associated with protection

from clinical disease, and it's been shown in adequate and well-controlled trials. The immunologic correlate of protection is most useful if a clear qualitative and quantitative relationship can be determined, so that you know that a certain level of immune response correlates with protection, as seen with the hepatitis B vaccine.

SLIDE 16

Examples of licensed vaccines with an identified correlate of protection would be the Hemophilus 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 would be the acellular pertussis, typhoid, and tuberculosis, or BCG, vaccines. 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 down from an older population to a younger one.

SLIDE 17

The Animal Rule is the third way to gain a claim of efficacy. Evidence is needed to demonstrate the effectiveness of new drugs when human efficacy studies are not ethical or practical. This would apply to new drugs or biologics that are intended to treat or prevent life-threatening or serious conditions such as smallpox.

SLIDE 18

The animal study endpoint has to be clearly related to the desired benefit in humans, and generally it will be the enhancement of survival or prevention of major morbidity. Animal challenge models may be used, such as a nonhuman primate with a particular orthopox virus delivered by challenge routes like intranasal, inhalation, or intravenous. The data or information of the kinetics and the pharmacodynamics of the product or other relevant data and information in the animals and humans allows for selection of an effective dose and then a challenge study in animals.

SLIDE 19

FDA can approve a product for which human safety has been established and the animal rule requirements are met. Even if a Sponsor demonstrates efficacy in an animal model, they still have to provide safety data in humans. The size of the safety population required for vaccine licensure is generally around 3,000 to 5,000 healthy subjects.

SLIDE 20

All studies subject to the Animal Rule have to be conducted in accordance with preexisting requirements under Good Laboratory Practice, called GLP, and the Animal Welfare Act. GLP will be required for the definitive pivotal animal studies, though it's not necessary for some of the earlier pilot phase studies. If data is

included in the label, then the study should have been conducted according to GLP.

SLIDE 21
The potential use of the Animal Rule would be in the development of vaccines for smallpox, anthrax, botulism, plague, tularemia, or Ebola and each product is reviewed on a case-by-case basis.

SLIDE 22
Now let's discuss safety monitoring in vaccine clinical trials. The goals are to protect 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 one, phase two, and phase three clinical trials.

SLIDE 23
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 -- the case report forms and the diary cards. For vaccines that are going into a healthy population, it is recommended using a toxicity grading scale for normal healthy adults. CBER found that sponsors were using toxicity grading scales that had been used in HIV and cancer trials. So, CBER 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.

Scripted interviews can be used. 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 24
Toxicity grading scales have been discussed.

A data safety monitoring board in phase one is not required except for clinical studies in children.

As for stopping rules, those 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 25
How can CBER assist regulatory authorities in developing countries to gain access to vaccines critical to their populations?

CBER is encouraging Sponsors to submit INDs. CBER can be involved in the early product review, the preclinical toxicology testing, and the clinical protocol design, and can help with the statistical analysis plan. Even if the FDA is only involved in phase one and phase two studies and the Sponsor later decides to go outside of the IND process for phase three, the Sponsor could still share the FDA's advice with foreign National Regulatory Authorities, or NRAs.

WHO has been involved in something called joint review where they have fostered collaboration between some of the less developed regulatory authorities and the European Medicines Agency, the EMA, which has assisted in reviewing phase three protocols, for example, malaria vaccine trials that are going to be conducted overseas.

SLIDE 26
What are the advantages for submitting an IND if a Sponsor has no intent to market its vaccine in the U.S.?

The advantages are that FDA can provide input on factors such as endpoint development, safety monitoring and assessment, clinical trial design, statistical analysis plans, product manufacturing, and quality testing and assay validation.

SLIDE 27
Does the FDA have a process whereby scientific advice and guidance on clinical product development can be given to a sponsor who may not plan to ultimately license a vaccine in the U.S.? Again, the Sponsor can use FDA's established IND process.

SLIDE 28
Has CBER licensed vaccines targeted against diseases not in the U.S.? Yes. CBER has licensed typhoid, Japanese encephalitis, and H5N1 influenza vaccines. The slide cites Section 351 of the Public Health Service Act, which allows FDA to do that.

SLIDE 29

Does CBER accept surrogate endpoints for clinical trials of vaccines against diseases or conditions not found in the U.S.? Yes.

A surrogate endpoint is one that would be expected to predict clinical benefit or harm or lack of benefit. It must also be based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence. An example of a surrogate endpoint would be what was used for the Human Papillloma Virus, or HPV, vaccine trials, where you don't want to wait years to meet an endpoint of full-blown cervical cancer. So instead, an advisory committee meeting was convened where experts discussed and accepted surrogate endpoints for end-stage cervical cancer in HPV vaccine clinical trials, because preventing development of these "surrogate" conditions was believed to be an endpoint considered reasonably likely to predict benefit.

SLIDE 30
There are mechanisms in place to facilitate product development for vaccines with high public health impact, and here are three ways that you can develop a product if it has high public health impact. This would include accelerated approval that has been used for the influenza vaccines, fast track, and priority review.

SLIDE 31
FDA can grant accelerated approval based on a determination that the effect of the surrogate endpoint is reasonably likely to predict clinical benefit. For influenza it may be reaching an immune response titer of greater than or equal to 1 to 40, and a fourfold rate of seroconversion.

SLIDE 32
The 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 benefit. It is described in the FDA Modernization Act. An example of a surrogate endpoint would be what was already discussed regarding HPV vaccine development.

SLIDE 33
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 this type of cancer or this 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 34
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 two, and pre-BLA meetings are strongly recommended. It's all designed to expeditiously get these very important products to market.

SLIDE 35
Products that are regulated by CBER are eligible for priority review if they provide a significant improvement compared to already marketed products. This is a 6-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 CBER is also going to give it a priority review. An example of a product that would merit a priority review would be the 7-valent pneumococcal vaccine, Prevnar.

SLIDE 36
Will CBER grant priority review to a BLA submitted for a vaccine indicated for a disease not endemic to the U.S.?
Yes, if appropriate criteria are met. Vaccines to prevent diseases such as malaria, tuberculosis, and HIV would be considered very important products.

SLIDE 37
Does CBER require that pivotal studies for vaccine licensure be conducted in the U.S. population?

No, we do not require this and it was not required for licensure of the rotavirus vaccine, ROTARIX. However, the Sponsor did need to provide data in the U.S. population, because with pediatric vaccines, CBER needs to ensure that there is no immune response interference when US children receive the study vaccine along with other US licensed vaccines that are given on the US schedule. The U.S. uses a different vaccine schedule, and may use different vaccines than the WHO and other countries. The US does not use BCG or oral polio vaccine.

For example, rotavirus vaccines may have a different safety and efficacy profile when administered with a live oral polio vaccine.

SLIDE 38
Foreign clinical data from supportive and confirmatory trials are acceptable. This slide includes the Code of Federal Regulations citations.

It is expected that clinical trial design and conduct should be applicable to the U.S. population and be performed with qualified investigators. Data validation using onsite inspections or other means will have to be done. It is also important to document conformance with ethical principles.

Clinical studies have to be adequate and well controlled if FDA is going to accept them to support licensure.

SLIDE 39

There is an ICH guidance E5 that you can review regarding ethnic issues and other factors related to the acceptability of foreign clinical data.

SLIDE 40
"Bridging studies" are often used. This is a supplemental study performed in a new region which will provide clinical data to bridge to this particular population. You can do bridging studies for efficacy based on immune response criteria, and for safety in a new population.

SLIDE 41
Considerations for foreign clinical trials include being cognizant of efficacy and immunogenicity differences in populations and making sure that all of the clinical data is collected appropriately, with use of appropriate case definitions and sample size.

SLIDE 42
An example where foreign data would play an important role would include cholera vaccine development.

SLIDE 43
Does CBER require that all foreign studies be done under IND?
No, foreign studies do not all have to be done under IND.

SLIDE 44
Foreign clinical studies not conducted under IND are accepted if they are relevant, well designed, and well-conducted in an ethical way.

SLIDE 45
Can a sponsor submit a BLA without any expectation of marketing the vaccine in the U.S.?

Yes, they can. However, the absence of U.S. marketing intent does not affect the user fees. So, they would still have to pay a user fee. There are conditions and circumstances where a user fee can be waived. The slide shows the web link, if you have additional questions.

SLIDE 46
Are population bridging studies needed if the safety and efficacy data to support licensure of the vaccine are from pivotal studies? It really depends on the indication that's being sought.

SLIDE 47
Here are some types of bridging studies that may need to be done for a product seeking an indication in a new population or age group.

SLIDE 48

This slide continues with more bridging study types.

SLIDE 49
When you do a bridging study you want to keep the comparison groups similar on demographics, medical practice and conduct of the trial.

SLIDE 50
There are other issues that will not be discussed here, but you should be aware of them. These include: co-administration, human challenge studies, adjuvants, and pediatrics.

If a challenge model will be used to support licensure, it would be very important to submit the protocol for the challenge model to FDA, so it can be reviewed and comments can be presented.

Adjuvant issues have already been discussed.

There are also specific issues for pediatrics. FDA has regulations so that products should not go into children unless it is sure that there is some prospect of benefit.

SLIDE 51
Early consultations are recommended so FDA can address issues with co-administered vaccines.

SLIDE 52
For human challenge studies, chemistry, manufacturing and controls, called CMC, information is needed on the challenge organisms to be utilized.
The challenge model should be developed under IND to ensure that it will be an appropriate indicator for assessment of vaccine activity.

For example, 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 U.S. 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 53
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, the recently published Draft 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 54
There are regulations regarding the protection of human subjects in the Code of Federal Regulations, shown here.

SLIDE 55
Updates on Pediatrics and the FDA Amendment Acts of 2007 are:
The Pediatric Medical Device Safety and Improvement Act of 2007;
The Pediatric Research Equity Act of 2007; and
The Best Pharmaceuticals for Children Act of 2007.

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 56
This slide has additional information on pediatric vaccine development and PREA.

SLIDE 57
In summary, CBER 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 IND process supports this endeavor.

SLIDE 58

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.