Guidance for Industry

General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit written comments on this guidance at anytime to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the title of this guidance.

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (OCTMA) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact OCTMA at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

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General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases

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I. INTRODUCTION

In this guidance, we, FDA, provide information to assist sponsors in developing vaccines to protect against global infectious diseases. The guidance will focus on development and licensure of vaccines targeted against infectious diseases or conditions endemic in areas outside the United States. In addition, the guidance will clarify regulations, statutes and guidances applicable to the development of these products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The development of safe and effective vaccines to protect against global infectious diseases (e.g., tuberculosis, malaria, human immunodeficiency virus/acquired immunodeficiency syndrome (AIDS)), and enteric diseases is of critical public health importance. Development and availability of such vaccines, particularly for use in the developing countries most affected by these diseases, will benefit U.S. and global health.

This document provides general recommendations for regulatory pathways to use in the development of vaccines to protect against global infectious diseases for U.S. licensure and clarifies applicable regulations.[1] This guidance also clarifies several misconceptions

[1] This guidance will not address details of clinical trial design, clinical trial conduct, endpoints, and statistical analysis as these are specific to the product and indication. For general guidance on these topics, we recommend that you consult relevant FDA guidances (See http://www.fda.gov/cber/guidelines.htm) and the following International Conference on Harmonisation (ICH) guidances: E8 General Considerations for Clinical Trials, E9 Statistical Principles for Clinical Trials, and E10 Choice of Control

surrounding the development of vaccines to protect against global infectious diseases in regard to U.S. regulatory requirements. These clarifications are intended to ensure that potential sponsors and vaccine manufacturers understand that a) FDA can license vaccines to protect against infectious diseases or conditions not endemic in the United States; b) the regulatory pathways to U.S. licensure for the development of vaccines to protect against infectious diseases not endemic in the U.S. are the same as for vaccines to protect against diseases that are endemic in the United States; and c) sponsors may submit data from clinical trials conducted outside the United States to support product licensure.

III. APPLICABLE REGULATIONS AND LEGISLATION

Current authority for the licensure and regulation of vaccines resides in section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) and numerous sections of the Federal Food, Drug, and Cosmetic Act (FFD&C Act). Section 351 of the PHS Act provides FDA with the authority to approve marketing applications for biological products intended to treat, mitigate, diagnose, or prevent conditions or diseases found in the United States or primarily endemic to other countries. In the Food and Drug Administration Amendments Act of 2007, which amends subchapter A of chapter V of the FFD&C Act (21 U.S.C. 351 et seq.) by adding section 524, Congress recognized the importance of having products to treat and prevent tropical diseases that disproportionately affect poor and marginalized populations and for which there is no significant market in developed nations. Under section 524, the Agency can grant priority review of applications under section 505(b)(1) of the FFD&C Act or section 351 of the PHS Act for the 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 and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary."

The laws and regulations for the licensure of vaccines to protect against global infectious diseases apply to diseases endemic in areas outside the United States as well as diseases endemic in the United States. Under section 351 of the PHS Act, BLAs are approved if data show that the product is "safe, pure and potent," and that the manufacturing facility meets standards designed to assure that the biological product "continues to be safe, pure, and potent." In the FDA guidance entitled, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" dated May 1998 (Ref. 7) (section II.A.), FDA noted that

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Group and Related Issues in Clinical Trials (Refs. 1, 2, and 3). Sponsors should contact the Center for Biologics Evaluation and Research (CBER) for additional information about these aspects of vaccine development.

Advances in biotechnology have resulted in novel vaccines that are presently developed to protect against global disease (e.g., nucleic-acid based (DNA) vaccines, viral-vectored vaccines, recombinant fusion protein vaccines and genetically altered attenuated live vaccines). These vaccines are frequently combined with novel adjuvants and administered using new delivery systems (e.g., needle-less injection). Therefore, successful nonclinical safety evaluations are an important step in evaluating vaccines before proceeding with clinical development and are discussed in references 4 and 5. Furthermore, chemistry, manufacturing, control and inspection of the manufacturing facility needed for licensure are critical aspects of the biologics license application (BLA) and are addressed in the FDA guidance entitled, "Guidance for Industry: Content and Format of Chemistry, Manufacturing, and Controls Information and Establishment Description Information for a Vaccine or Related Product" (Ref. 6). We encourage sponsors to discuss with us these aspects of product development during the Investigational New Drug Application process.

potency has long been interpreted to include efficacy (21 CFR 600.3(s)). Proof of effectiveness generally consists of controlled clinical investigations as defined in the provision for 'adequate and well-controlled' studies for new drugs (See 21 CFR 314.126).

The regulatory requirements contained in title 21 of the Code of Federal Regulations (21 CFR) apply to all vaccines licensed in the United States, regardless of their indication or intended target population. These regulations establish the methods and standards for manufacturing a biological product to assure that the product is safe and meets the quality and purity characteristics that it claims to possess (21 CFR Parts 600 through 680). These regulations also cover the type of clinical studies that should be performed during product development (e.g., 21 CFR Parts 50, 56, and 312).

Accelerated approval may be granted for certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (21 CFR Part 601, Subpart E).

21 CFR 601.41 sets forth the following requirements for accelerated approval:

1) Approval will be based on adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.

2) Approval will be subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate outcome.

3) Postmarketing studies, intended to verify the clinical benefit of the product, usually would be underway already, at the time of approval. Such studies must be adequate and well-controlled and conducted with due diligence. The protocols for these studies should be submitted with the original BLA. Marketing approval for biological products approved under 21 CFR 601.41 or 601.42 may be withdrawn, for example, if the postmarketing clinical study fails to verify clinical benefit or the sponsor fails to perform the required postmarketing study with due diligence (21 CFR 601.43(a)(1) and (2)).

In May 2002, FDA published a final rule entitled "New Drug and Biological Drug Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible" (Ref. 8). Under this rule, the agency amended its new drug and biological product regulations to allow appropriate studies in animals in certain cases to provide substantial evidence of the effectiveness of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances (21 CFR Part 601, Subpart H). This rule applies when definitive human efficacy studies are not ethical or feasible. In these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions and for which safety has been established may be approved for marketing based on evidence of effectiveness derived from adequate and well-controlled studies in animals. In assessing the sufficiency of animal data, the agency may take into account other data.

IV. DEVELOPMENT OF VACCINES TO PROTECT AGAINST GLOBAL INFECTIOUS DISEASE

FDA is encouraging sponsors to develop and license vaccines to protect against global infectious diseases by submitting an Investigational New Drug Application (21 CFR Part 312), even if the U.S. market for that vaccine may be limited and the primary target populations for the vaccine are in developing countries. Sponsors who are interested in developing these vaccines should begin interactions with the agency early in product development, such as through pre-IND meetings. Procedures and policies for the conduct of meetings with CBER are summarized in the FDA Guidance entitled, "Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products" (Ref. 9).

The clinical development pathway for a vaccine to protect against a global infectious disease depends on its indication and target population and thus; the study population, laboratory and clinical evaluation, trial design and endpoints chosen are specifically tailored to the product. In general, the clinical immunogenicity, safety and effectiveness of a vaccine are evaluated in various phases of study conducted under an IND as defined in 21 CFR 312.21. Phase 3 trials provide the critical documentation of the vaccine's effectiveness and important additional safety data required for licensure. Thus, prior to initiating Phase 3 clinical trials, we recommend that you discuss with us the details related to study conduct (e.g., issues related to the disease to be prevented or treated, study site(s), subject selection, choice of control group, trial design parameters such as endpoints/case definitions and diagnostic tests, dose and dosing schedule, study duration, concomitant vaccinations and medications, as well as safety assessments) well in advance of study initiation to ensure that these studies are adequately designed to meet their stated objectives and to support product licensure. These trials should be conducted under the provisions of good clinical practice (GCP). For FDA regulations relative to GCP and clinical trials, we refer you to the FDA website www.fda.gov/oc/gcp/regulations.html.

A. Foreign Clinical Studies

For vaccines to protect against global infectious diseases, foreign efficacy trials are likely to be necessary if the disease of interest has a low incidence in the United States. There may also be a situation where the vaccine is developed primarily for a market outside the United States. FDA has licensed vaccines based on efficacy data derived from studies solely in disease endemic countries (e.g., typhoid vaccine, hepatitis A vaccine, Japanese encephalitis vaccine, and several acellular pertussis vaccines).

FDA regulations permit the acceptance of foreign clinical studies in support of a BLA approval, provided certain conditions are met. Foreign studies performed under an IND must meet the requirements of 21 CFR Part 312. 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, including that the study was conducted in accordance with GCP and including review and approval by an independent ethics committee (Ref. 10). For further guidance on general principles for the conduct, performance and control of clinical trials, refer to ICH documents E6: Good Clinical Practice: Consolidated

Guideline and E8: Guidance on General Considerations for Clinical Trials (Refs. 1, 11). In addition, it is important to assess the impact of ethnic factors on the vaccine's safety and effectiveness. These principles are discussed in the ICH document E5: Ethnic Factors in the Acceptiblity of Foreign Clinical Data (Ref. 12).

B. Human Challenge Studies

In some situations, it may be possible to conduct challenge studies in human subjects during early development or in lieu of clinical trials in an endemic area. Such studies may be conducted to demonstrate "proof of concept" of the vaccine antigen early in clinical development (e.g., *Plasmodium falciparum* sporozoite challenge of malaria-naïve U.S. volunteers previously administered a candidate malaria vaccine). Human challenge studies may also be conducted to demonstrate the efficacy of the vaccine. For example, in 1993 and 1998, the agency 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, who are at high risk for contracting the disease. In 1998, the committee agreed that human challenge studies could suffice to demonstrate efficacy of a cholera vaccine provided that studies were adequate and well-controlled and conducted under the provisions of GCP (See ref. 13). Of note, use of challenge studies to demonstrate efficacy does not preclude the requirement for adequate safety data. As human challenge studies may present unique considerations, we recommend that the sponsor discuss its development plan with CBER prior to initiation of such studies for either proof of concept or vaccine efficacy.

C. Pediatric Development

Vaccine development generally takes place in a stepwise fashion from adults to children. However, for many global diseases (e.g., malaria), the pediatric population may face greater mortality or morbidity than the adult population because adults may already be immune. Therefore, it may be appropriate or necessary to start development in infants or children. For pediatric studies in the United States, institutional review boards must ensure research is compliant with 21 CFR Part 50, Subpart D. The Pediatric Research Equity Act (PREA)[2] addresses product development for pediatric uses. PREA requires pediatric assessments to be included in all applications submitted under section 505 of the FFD&C Act or under section 351 of the PHS Act, unless the sponsor has obtained a waiver or deferral from FDA. If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric subjects, such as immune response studies (section 505B(a)(2)(B) of the FFD&C Act). Sponsors must also submit adequate safety information to support use in the pediatric population.

[2] Reauthorized in Title IV of the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85).

V. FREQUENTLY ASKED QUESTIONS

1. What is the regulatory path forward to U.S. licensure of a vaccine to protect against an infectious disease that is not endemic to the United States?

The regulatory path for a vaccine to protect against an infectious disease that is not endemic or in existence in the United States is the same as for a vaccine to protect against a disease that exists in the U.S. population. In addition to traditional approval, two other pathways for approval may be utilized. First, accelerated approval may be granted using a surrogate endpoint or a clinical endpoint other than survival or irreversible morbidity for a biological product used to treat a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments (21 CFR Part 601, Subpart E). Approval may be subject to conducting post-marketing studies to verify the biological product's clinical benefit, when required to be conducted. Second, approval may be granted based on evidence of effectiveness from studies in animals when human efficacy studies are not ethical or feasible (21 CFR Part 601, Subpart H). In such cases, after approval, a sponsor must conduct post-marketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated in circumstances where such studies are feasible and ethical; such post-marketing studies would not be feasible until an exigency arises (21 CRF 601.91(b)(1)).

2. How does a sponsor start interactions with CBER to develop a vaccine to protect against a global infectious disease?

CBER encourages all sponsors that are interested in developing vaccines to begin interactions with us early in development, such as through pre-IND meetings (Ref. 9). Please call the Division of Vaccines and Related Products Applications at 301-827-3070.

3. Has CBER licensed vaccines to protect against global infectious diseases that are not endemic or have not been reported in the United States?

Yes. CBER has licensed vaccines for diseases not endemic or in existence in the United States. These vaccines, including vaccines against typhoid, Japanese encephalitis, and H5N1 influenza virus, include indications for individuals living in or traveling to endemic areas.

4. Are the licensure requirements for a vaccine intended to be used primarily in other countries the same as the requirements to license a vaccine for use in the United States?

Yes. The requirements for CBER to license a vaccine include a demonstration that 1) the vaccine is safe, pure, and potent (safe and effective) and 2) the facility in which the vaccine is manufactured complies with current good manufacturing practice. The level of evidence necessary to demonstrate the safety and effectiveness of the vaccine is the same whether or not the disease, for which the vaccine is indicated, is endemic to the United States.

5. Does CBER accept surrogate endpoints for clinical trials of vaccines intended to protect against global infectious diseases not found in the United States?

Yes. If a surrogate endpoint is reasonably likely to predict clinical benefit, CBER can accept that endpoint for use in clinical trials for licensure if the product is for a serious or life-threatening illness and provides meaningful therapeutic benefit to patients over existing treatments. CBER may approve a BLA under the accelerated approval regulations (21 CFR Part 601, Subpart E) with the requirement that post-marketing studies be performed to verify the clinical benefit of the product.

6. What does U.S. licensure signify?

A U.S. license signifies to the global medical and regulatory community that the FDA has made the determination that the vaccine is safe and effective. This finding by the FDA may assist other National Regulatory Authorities in their evaluation of the vaccine.

7. How does the submission of an IND assist sponsors in the development of vaccines to protect against global infectious diseases?

FDA encourages submission of an IND so that it can provide input on manufacturing, quality testing, assay validation, non-clinical and clinical trial design issues, statistical analysis plans, endpoints, and other important aspects of vaccine development. The IND process will allow sponsors to obtain important scientific and regulatory advice on products that are critical to the advancement of world health.

8. Is there a user fee for IND submissions?

No. There is no user fee for pre-IND and IND submissions or activities related to the IND, such as meetings and feedback from CBER to the sponsor.

9. Does CBER require that studies to support vaccine licensure be conducted in the U.S. population?

There is no such requirement. CBER evaluates trials conducted outside the United States to determine if the vaccine is safe and effective for use as proposed in labeling. As part of this evaluation, CBER considers factors such as disease epidemiology, the study population, and the environmental and medical care conditions. If studies to support vaccine licensure are conducted outside the United States, CBER may request a smaller U.S. study that bridges immunogenicity and/or safety to the U.S. population.

10. Does CBER require all foreign studies to be conducted under an IND to support approval of a BLA?

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, including that the study was

conducted in accordance with GCP, including review and approval by an independent ethics committee.

11. Is a sponsor who submits a BLA required to pay an application user fee even if the sponsor does not intend to market the product in the United States?

Yes. The sponsor is required to pay a user fee regardless of whether the sponsor intends to market the licensed product in the United States. However, sponsors may have the application user fee waived if they meet certain criteria, such as being a small business entity or having an orphan designation for their product. For more information on user fees and waivers, see: http://www.fda.gov/cder/about/smallbiz/pdufa.htm.

12. Are vaccines to protect against global infectious diseases not found in the United States eligible for orphan designation?

Yes. A sponsor may apply for designation of its vaccine as an "orphan drug" if the vaccine is intended for use against a rare disease or condition. Orphan drug designation is based on the disease prevalence in the United States and qualifies a sponsor to receive certain benefits from the Government in exchange for developing the vaccine for a rare disease or condition. For example, a BLA for a vaccine that has been granted orphan designation is not subject to an FDA user fee unless the vaccine application includes an indication other than for a rare disease or condition. Orphan designation also qualifies the sponsor or applicant for a tax credit and marketing incentives under the Orphan Drug Act. In addition, a sponsor of a vaccine against a rare disease or condition may apply for grant support for clinical trials of the vaccine under the Office of Orphan Products Development Grant Program. Designation as an orphan drug is not a requirement for consideration for support under this grant program. Please note that a vaccine designated as an orphan product must be evaluated for safety and efficacy like any other vaccine. For more information, please contact the FDA Office of Orphan Products Development at 301-827-3666 or http://www.fda.gov/orphan/index.htm.

VI. REFERENCES

1. International Conference on Harmonisation (ICH); E8: General Considerations for Clinical Trials, December, 1997.

2. ICH; E9: Statistical Principles for Clinical Trials, September 1998.

3. ICH; E10: Choice of Control Group and Related Issues in Clinical Trials, May, 2001.

4. World Health Organization. WHO guidelines on nonclinical evaluation of vaccines. Annex 1. WHO Technical Report Series. 2005; 927:31-63. www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/en/.

5. Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications, February 2006 (http://www.fda.gov/cber/gdlns/reprotox.htm).

6. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product, January 1999 (http://www.fda.gov/cber/gdlns/cmcvacc.htm).

7. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998 (http://www.fda.gov/cber/gdlns/clineff.htm).

8. Final Rule, New Drug and Biological Drug Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Efficacy Studies are Not Ethical or Feasible, 67 FR 37988, May 31, 2002.

9. Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products, February 2000 (http://www.fda.gov/cber/gdlns/mtpdufa.htm).

10. Final Rule, Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, 73 FR 22800, April 28, 2008 (http://www.fda.gov/cber/rules/forclinstud.htm).

11. ICH; E6: Good Clinical Practice: Consolidated Guideline, May 9, 1997.

12. ICH; E5: Ethnic Factors in the Acceptibility of Foreign Clinical Data, June 10, 1998.

13. Vaccines and Related Biological Products Advisory Committee meeting, May 26-27, 1998 (http://www.fda.gov/ohrms/dockets/as/98/transcpt/3422t2a.pdf).