Guidance for Industry

Development of Preventive HIV Vaccines for Use in Pediatric Populations

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 any time 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.fda.gov/dockets/ecomments. 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 (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 the Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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I. INTRODUCTION

In this guidance, we, FDA, provide recommendations to sponsors regarding data to support the: 1) Initiation of pediatric studies of a preventive HIV vaccine under a United States (U.S.) investigational new drug application (IND); and 2) licensure of a preventive HIV vaccine for pediatric use. We also provide recommendations to investigators and institutional review boards (IRBs) who are involved with these pediatric studies.[1]

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. SCOPE

This guidance directs sponsors and investigators to the regulations, statutes, and guidances that outline the special considerations for conducting clinical studies in pediatric populations. These documents apply to developing and licensing preventive HIV vaccines for use in pediatric populations.

[1] The Congressional reports accompanying the Agricultural, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2006, Public Law No. 109-97 (enacted November 10, 2005), urged FDA to issue guidance within six months addressing "the minimum requirements for obtaining approval of the Food and Drug Administration to test an HIV vaccine in pediatric populations and the minimum requirements for obtaining Food and Drug Administration approval of a pediatric indication of an HIV vaccine." House Report 109-102 at 80-81 (2005). *See also* Senate Report 109-92 at 153-154 (2005) (containing nearly identical language). This guidance responds to these requests.

This guidance specifically addresses issues regarding developing a preventive HIV vaccine for use in healthy U.S. pediatric populations. Because the prevalence of HIV infection in these populations is low, the risks presented by studies on these pediatric subjects would need to be commensurately low. Studies of prevention of vertical transmission of HIV and of transmission via breastfeeding in neonates and infants, which are of worldwide public health importance, will be difficult to conduct in the U.S. due to the low prevalence of transmission of HIV through these routes of exposure in the U.S. population.[2]

In the U.S, it is likely that a safe and effective HIV vaccine would be used to prevent HIV transmitted by sexual or blood exposure; thus, the pediatric population most at risk for such transmission would be adolescents. Therefore, clinical studies conducted to support use in the U.S. would likely target these pediatric age groups and are the focus of this guidance.

III. BACKGROUND

Vaccine development in the U.S. generally takes place in a stepwise fashion from adults to children. This development pathway has led to the licensure of numerous pediatric vaccines over the past decade, including new vaccines against whooping cough, chickenpox, hepatitis A, pneumococcus, influenza, and meningococcus. The same development pathway applies to HIV vaccines. At this time, however, the greatest challenge to developing safe and effective HIV vaccines in any population, including pediatric populations, is the need for additional scientific knowledge. For example, to date, no studies of investigational HIV vaccines have demonstrated protection against HIV infection, and the immune responses associated with protection against HIV infection have not been identified.

Federal statutes, FDA regulations, and FDA guidances contain helpful information to guide the scientific conduct of studies in pediatric populations, as well as issues of human subject protection, including special protections afforded pediatric populations. Specifically, the Pediatric Research Equity Act of 2003 (PREA)[3] addresses drug and biological product development for pediatric uses. In addition, we have issued guidance on the Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11) to facilitate pediatric product development (Ref. 1).

Pediatric Regulations and Legislation

Under PREA, all applications (or supplements) submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration are to contain a pediatric assessment unless the

[2] If such studies are conducted outside the U.S. under a U.S. IND, the sponsor, investigators, and IRB must comply with the U.S. IND as well as applicable provisions of FDA regulations addressing INDs (21 CFR Part 312), protection of human subjects (21 CFR Part 50), and the conduct of IRBs (21 CFR Part 56), in addition to local regulations. See 21 CFR 312.120 for information on FDA acceptance of foreign clinical studies *not* conducted under an IND.

[3] Pediatric Research Equity Act (Public Law 108-155).

sponsor has obtained a waiver or deferral from FDA. We issued a draft guidance on the implementation of PREA in September 2005 (Ref. 2). As stated in that document, we encourage the submission of pediatric development plans to FDA as early as possible in the vaccine development process.

Given the current stage of development of preventive HIV vaccines and the lack of understanding about immunity to HIV, scientific and ethical issues are paramount when considering the timing, design, and conduct of studies of HIV vaccine candidates in pediatric populations. Under FDA and Department of Health and Human Services regulations, children are considered a vulnerable population requiring additional protections as research subjects.[4] Specifically, 21 CFR Part 50, Subpart D, "Additional Safeguards for Children in Clinical Investigations" provides the framework for IRBs to follow when making decisions about clinical investigations in children.[5] These regulations contain provisions for soliciting permission from parents or guardians and for obtaining assent from children participating in clinical studies.[6] The FDA Pediatric Ethics Working Group has summarized the discussion of the November 15, 1999, Pediatric Advisory Subcommittee meeting on ethical issues relating to clinical studies in healthy children. The conclusions can be found at http://www.fda.gov/cder/pediatric/ethics-statement.htm.

Sponsors and investigators should familiarize themselves with the PREA requirements, the regulations described above applicable to the conduct of studies in pediatric populations, and FDA guidances that address issues of pediatric studies in drug and biologics development.

IV. DATA TO SUPPORT PEDIATRIC STUDIES OF INVESTIGATIONAL PREVENTIVE HIV VACCINES

A. Preclinical/Nonclinical Studies

Requirements for reproductive toxicity, genotoxicity, or carcinogenicity studies, and the timing of these studies in relationship to the initiation of pediatric studies, would be made on a case-by-case basis, and would be based upon the data available from previous animal and human studies of the investigational vaccine.[7] We encourage sponsors to seek input from FDA in pre-IND meetings or other early communication regarding appropriate non-clinical studies to support pediatric studies.

B. Amount and Kinds of Adult Data

The amount and kinds of the adult data needed to support initiation of pediatric studies will depend upon:

- The strength of the adult safety and immunogenicity data generated;

[4] See 21 CFR Part 50, 21 CFR 56.111, and 45 CFR 46.111.
[5] See also 45 CFR Part 46, Subpart D.
[6] Title 21 CFR 50.55.
[7] See 21 CFR Part 312.

- what is known about the investigational vaccine in terms of its relationship to well-characterized vaccines or novel vectors or production methods; and
- the relationship of documented immune responses to protection.

It is very important to have adult safety and activity data prior to the initiation of pediatric clinical studies of an HIV vaccine. These adult data will provide the basis for selecting an appropriate starting dose and schedule for pediatric populations. Safety data in adults should be obtained from carefully monitored studies with pre-specified safety assessments. Sponsors should assess clinical chemistry and hematology parameters in at least one adult study prior to initiating pediatric studies.[8] The safety profile of the vaccine, the adjuvant used, and the maturity of immune responses in the targeted age group are important factors that influence the optimal dose and schedule for use in pediatric populations. Sponsors should include the available adult data with any IND submission that includes a pediatric protocol.[9]

C. Additional Considerations

1. Choice of Pediatric Age Group

Sponsors should take into account the mode of transmission of HIV and risk of HIV infection in choosing the pediatric age groups that will be studied, and should provide their rationale for the choice of age group in their IND submissions (Ref. 1). Sponsors who wish to use an age cut-off to define an adolescent age group should explain the chosen age(s), taking into consideration the multiple factors that may influence puberty. Evaluation in a stepwise fashion from oldest to youngest is anticipated for reasons of human subject protection.[10]

2. Safety Data

Safety data in pediatric studies should be rigorously collected, using pre-specified adverse event (AE) grading scales that are age-appropriate (Ref. 1).[11] Local and systemic reactogenicity and other AEs, including serious and unexpected adverse drug experiences as defined in 21 CFR 312.32, should be evaluated in each study. The kinds of safety data prospectively gathered should be based upon the characteristics of the investigational vaccine (e.g., DNA vaccine, live viral vectored vaccine, adjuvanted vaccine) and should also specifically evaluate AEs identified in the adult studies.[12] Pediatric subjects enrolled in vaccine studies should be followed for the occurrence of serious and unexpected AEs and the new

[8] Title 21 CFR 312.23.
[9] See 21 CFR 312.23.
[10] *See, e.g.*, http://www.fda.gov/cder/pediatric/ethics-statement.htm.
[11] See also FDA Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, April 2005 (http://www.fda.gov/cber/gdlns/toxvac.pdf). This draft guidance, when finalized, will represent FDA's current thinking on that topic.
[12] Title 21 CFR 312.23.

onset of medically significant diseases. Typically, this is done for at least six months after the last dose.

3. Blood Sampling/Assays

We recommend that blood sampling for safety laboratory evaluations and immunogenicity assessments be minimized to decrease distress associated with venipuncture (Ref. 1). Assays to measure the immune response to HIV vaccines should be developed in adults prior to their use in evaluating pediatric immune responses, and these may need to be modified for the purpose of testing small volumes of blood.

4. Special Concerns

HIV vaccine studies conducted in adult populations have raised concerns such as the potential for increase in risky sexual behaviors and false positive HIV test results. In adults, potential concerns related to a false positive HIV test may include discrimination in the workplace and other settings or the inability to donate blood. To address concerns such as these, studies in adults incorporate education on reducing sexual risks and documentation of effective contraception use to prevent vaccinating pregnant women. The potential implications for the pediatric subject of a false positive HIV test will require age-appropriate discussion at entry and throughout study enrollment, and should involve the parent/guardian.[13] Sponsors, investigators, and IRBs should consider concerns such as these in developing, reviewing, and implementing pediatric clinical studies.

Preventive HIV vaccine study informed consent forms and processes that have been developed for adults can serve as a starting model for addressing concerns such as these in pediatric populations. We recommend involving clinicians who have expertise in adolescent behavior and development, in the design and conduct of studies in adolescents.

V. DATA TO SUPPORT THE LICENSURE OF A PREVENTIVE HIV VACCINE FOR PEDIATRIC USE

Licensure of a preventive HIV vaccine for pediatric use may be sought as a BLA or as a supplement if there is a licensed HIV vaccine for adult use. Sponsors should support such BLA or supplement with adequate safety and effectiveness data.[14] FDA's "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products,"[15] dated

[13] Title 21 CFR 50.25 and 50.55.
[14] Sec. 351 of the PHSA (42 U.S.C. 262); sec. 505B(a)(2)(A) of the Act (21 U.S.C. 355c(a)(2)(A)) (added by PREA).
[15] See http://www.fda.gov/cber/gdlns/clineff.pdf.

May 1998, contains recommendations on the evidence to be provided in a BLA or supplement to demonstrate effectiveness.[16]

A. Using Adult Efficacy Data

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.[17] Extrapolation of adult data may be appropriate for evaluation of a preventive HIV vaccine intended to prevent transmission via sexual or blood (e.g., intravenous drug use) exposure. In such cases, efficacy in prevention of new HIV infections in adults supported by immunogenicity and safety data in children may be sufficient to support pediatric use of a preventive HIV vaccine. Identification of an immune response that is predictive of protection will facilitate extrapolation of efficacy from the adult population to pediatric populations.

B. Pediatric Efficacy Study with Clinical Outcomes

A pediatric efficacy study with clinical outcomes, e.g., documented HIV infection, can also be used to provide efficacy data to support licensure. Because of the low prevalence of HIV infection in pediatric populations in the U.S., such a study would likely be conducted in an area of high HIV prevalence outside the U.S. Foreign studies used to support U.S. licensure should be conducted according to good clinical practice. Good clinical practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical studies that enroll human subjects.[18] If foreign studies are conducted, we recommend early discussion with FDA to ensure that these foreign data will be acceptable to support vaccine use in the U.S. pediatric population, where the prevalence is lower and the most common routes of transmission differ from non-U.S. pediatric populations.

Sponsors wishing to submit to FDA pediatric efficacy data obtained in a foreign population also should conduct a clinical bridging study to permit extrapolation to the U.S. population for a similar pediatric use.[19] Identification of an immune response that is predictive of protection will facilitate extrapolation of efficacy from one population to another in these bridging studies. Extrapolation of data across regional prevalent types and subtypes of HIV may also need to be addressed.

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[16] For purposes of this guidance, as with the May 1998 guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical study or the intent of conducting such a study and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

[17] Sec. 505B(a)(2)(B)(i) of the Act (21 U.S.C. 355c(a)(2)(B)(i)) (added by PREA).

[18] ICH; FDA Guideline: E6 Good Clinical Practice: Consolidated Guideline (62 FR 25691-25709, May 9, 1997). See also http://www.fda.gov/cder/guidance/959fnl.pdf.

[19] ICH; FDA Guidance for Industry: E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data – Questions and Answers, June 2004 (http://www.fda.gov/cber/gdlns/iche5ethnic.pdf).

VI. REFERENCES

1. International Conference on Harmonisation; FDA Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population, December 2000 (http://www.fda.gov/cber/gdlns/ichclinped.pdf).

2. FDA Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act, September 2005 (http://www.fda.gov/cber/gdlns/pedreseq.pdf). This draft guidance, when finalized, will represent FDA's current thinking on that topic.