



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20852-1448

JUL 21 2008

William L. Driscoll  
Vaccine For All LLC  
5107 25<sup>th</sup> Road North  
Arlington, VA 22207

Re: Docket Number FDA-2006-P-0325 (formerly 2006P-0536/CP1)

Dear Mr. Driscoll:

This letter responds to your citizen petition (Petition) submitted to the Food and Drug Administration (FDA) on December 27, 2006 (Docket No. FDA-2006-P-0325, formerly 2006P-0536/CP1). You request, among other things, that FDA amend its regulations under 21 CFR 312.7 to allow a sponsor, whom FDA has permitted to begin Phase I clinical trials for a pre-pandemic or pandemic vaccine, to market and sell “Best Efforts” to produce and deliver an FDA approved pre-pandemic or pandemic vaccine. Your Petition provides specific suggestions for amending 21 CFR 312.7 that, if adopted, would allow the promotion, sale, and commercialization of “Best Efforts” concerning an investigational pre-pandemic or pandemic vaccine. You also request “an explicit FDA policy to permit those who purchase “Best Efforts” to purchase additional “Best Efforts” and donate any resulting FDA-approved vaccine to government or to a charity . . .”<sup>1</sup>

It is unclear what you mean by “Best Efforts.” Your Petition neither defines the term nor explains precisely what a “Best Efforts” transaction is in the context of FDA’s regulation of pre-pandemic or pandemic vaccines. This lack of clarity makes it difficult to determine how a “Best Efforts” regulatory scheme would operate practically and whether such a scheme would be within the scope of FDA’s jurisdiction, authority, and control, notwithstanding your proposed amendments to 21 CFR 312.7.

In addition, we consider ambiguous your definition of the term “pre-pandemic or pandemic vaccine.” Under “Action Requested” (page 2 of the Petition), you define pre-pandemic or pandemic vaccine “to include any H5N1 vaccine and any other vaccine to protect against an infectious disease with a case fatality rate of five percent or greater, as determined by World Health Organization statistics . . .” It is unclear whether your definition includes other influenza vaccine strains with pandemic potential or whether you are also referring to vaccines for non-influenza infectious agents with pandemic potential. Based on your Petition’s “Statement of Grounds” and the references cited in

<sup>1</sup> Page 2 of the Petition, first full paragraph, first sentence.

that section, we interpret your request to focus solely on pre-pandemic or pandemic influenza vaccine, rather than on any vaccine intended for any pandemic disease.

FDA has carefully reviewed and considered your Petition. Given the agency's understanding of your request and for the reasons set forth below, we deny your Petition.

## **DISCUSSION**

### **I. FDA DOES NOT REGULATE A SPONSOR'S EFFORTS TO OBTAIN FINANCING FOR RESEARCH AND DEVELOPMENT OF ITS PRODUCTS UNLESS SUCH EFFORTS INCLUDE PROMOTION OF AN UNAPPROVED PRODUCT**

FDA regulates vaccines under the authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) and under certain provisions of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 301 et seq.).<sup>2</sup> For example, FDA approves biologics license applications (BLAs) for pre-pandemic and pandemic influenza vaccines based on a demonstration that the vaccines are safe, pure, and potent and that the facilities in which the vaccines are manufactured, processed, packed, or held meet standards designed to assure that the products continue to be safe, pure, and potent.<sup>3</sup> FDA also regulates vaccine labeling, advertising, and promotional labeling (see Section 502 of the Act, and 21 CFR Parts 201 and 202); and, clinical investigations of vaccines in human subjects (see 21 CFR Part 312).

In order to uphold the integrity of the drug approval process and protect human subjects and potential patients, FDA prohibits the promotion of an investigational new drug as safe and effective (see 21 CFR 312.7(a)). Despite the restrictions on promotion under 21 CFR 312.7, FDA does not regulate a sponsor's efforts to obtain financing for the research and development of its products. Indeed, vaccine manufacturers and other interested parties are not precluded from soliciting and obtaining investment in investigational pre-pandemic and pandemic influenza vaccines, nor are they prohibited from entering into contracts concerning the delivery of pre-pandemic and pandemic influenza vaccine after FDA has approved a particular vaccine.

---

<sup>2</sup> FDA approves biologics license applications under section 351 of the Public Health Service Act. Most biological products, such as vaccines, are also “drugs” and therefore are subject to certain provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations (e.g., the investigational new drug application (IND) regulations, which include 21 CFR 312.7).

<sup>3</sup> Potency has long been interpreted to include effectiveness. (21 CFR 600.3(s)). Therefore, the BLA approval standards of safety, purity, and potency are similar to the Act's drug approval standards of safety and effectiveness. Indeed, Congress has directed FDA to minimize differences in the review and approval of products required to have approved BLAs and products required to have approved new drug applications under section 505(b)(1) of the Act. (FDA Modernization Act of 1997, Section 123(f)).

**II. TO THE EXTENT THAT 21 CFR 312.7 MAY BE APPLICABLE, FDA DECLINES TO ADOPT PETITIONER'S PROPOSED CHANGES TO 312.7**

A. Sale and commercialization of “Best Efforts” could undermine the approval process for pre-pandemic and pandemic influenza vaccines.

FDA regulations at 21 CFR 312.7 generally prohibit the sale and commercialization of an investigational new drug by a sponsor. As described in your Petition,<sup>4</sup> “Best Efforts” appear to involve the sale of pandemic influenza vaccine prior to FDA pre-market approval. Although the delivery of the vaccine would occur at some future and uncertain date and only if the sponsor received FDA approval, the actual sale of the vaccine would occur when the sponsor sells the “Best Efforts” when the vaccine is investigational and in development. The sale of “Best Efforts” would presumably create a legal obligation to deliver the vaccine to the purchaser (following FDA approval and the receipt of a second payment from the purchaser of the “Best Efforts”). The commercialization structure of the “Best Efforts” process could, therefore, create public demand for a vaccine before we have determined the vaccine’s safety and effectiveness.

Promotion of “Best Efforts” as described in your Petition could result also in a sponsor publicly disseminating information regarding the potential and unproven benefits of an investigational vaccine in Phase I clinical trials. Such information concerning the unapproved vaccine’s safety and effectiveness could be misleading because at the Phase I stage of the investigational drug development process, information on side effects, contraindications, and effectiveness is not available. Although the vaccine itself would not be commercially available to the public until FDA approval has been obtained, the promotion of “Best Efforts” could lead the sponsor to make statements about the vaccine that could be misleading, even if they include disclaimers.

Commercial demand for pandemic influenza vaccine before a determination of its safety and effectiveness has the potential to compromise the investigational process and create the appearance of conflicts of interest. Authorizing the sale of “Best Efforts” could create the appearance that FDA will approve investigational pre-pandemic and pandemic influenza vaccines that are subject to a “Best Efforts” transaction. If an entity believes that the agency has endorsed pre-pandemic and pandemic influenza vaccines still in the early investigational stages of development, that entity may more readily purchase “Best Efforts,” despite no guarantee that FDA will approve the vaccine. If a vaccine subject to a “Best Efforts” sale ultimately failed to gain FDA approval, the agency could be the subject of unjustified public criticism and baseless litigation by parties with a vested financial interest in the approval of such a vaccine. Such an appearance could undermine

---

<sup>4</sup> See, for example, page 1 of the Petition, third paragraph, first sentence, “Specifically, the requested policy would explicitly permit a sponsor, which had received FDA approval to begin Phase I clinical trials for a pre-pandemic or pandemic vaccine, to market and sell *best efforts* to produce and deliver FDA-approved pre-pandemic or pandemic vaccine (Best Efforts).”

FDA's ability to protect the public health, erode public confidence in FDA's role as an impartial regulator, and waste valuable agency resources.

B. Permitting the marketing and sale of “Best Efforts” would contravene FDA’s policy on charging for investigational new drugs.

In your Petition (page 3, paragraph (d) – Charging for and commercialization of investigational drugs), you propose amending the regulation at 21 CFR 312.7(d)(1) to add “This limitation does not apply to marketing and sale of best efforts to produce and deliver FDA-approved pre-pandemic or pandemic vaccine under 312.7(a).” Under 21 CFR 312.7(d)(1), a sponsor who wishes to charge for an investigational new drug in a clinical trial must provide FDA with a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial. In the preamble to the final rule as adopted, FDA explained that cost recovery is justified in clinical trials only when necessary to further the study and development of promising drugs that might otherwise be lost to the medical armamentarium (52 FR 19466 at 19474, May 22, 1987). The philosophy behind current 21 CFR 312.7(d)(1) was that FDA would authorize charging for an investigational drug in a clinical trial only in exceptional circumstances and would need evidence to show that the study for which charging is requested is necessary to further the development of the drug and could not be conducted without charging (71 FR 75168 at 75170, December 14, 2006).<sup>5</sup>

Although the Petition suggests that charging for “Best Efforts” would provide a general benefit of generating funds for research of pandemic influenza vaccines, the “Best Efforts” concept, as we understand it, is inconsistent with FDA's policy concerning charging for investigational new drugs in clinical trials. The Petition has not established why charging is necessary in order for a sponsor to develop pandemic influenza vaccine, and has failed to explain why the cost of developing a vaccine for the market should not be considered a sponsor's normal cost of doing business. Moreover, under the current regulation, FDA decides whether a sponsor can obtain cost recovery by charging for an investigational new drug on a case by case basis, while your proposal would permit the sale of “Best Efforts” for a certain class of pandemic and pre-pandemic vaccines.

Although the Petition states that it has identified a significant supply of “Best Efforts” through preliminary communications with biotechnology and pharmaceutical firms developing pandemic influenza vaccine, it fails to present evidence, financial or otherwise, that the sale of “Best Efforts” is necessary to further the development of investigational pandemic influenza vaccine and also fails to present any evidence that the development of pandemic influenza vaccine would not be conducted unless sponsors could obtain funds from the sale of “Best Efforts.” As you may be aware, in December

---

<sup>5</sup> Ethical considerations underlie FDA's policy against charging for investigational drugs. Because research subjects who participate in a clinical trial are permitting themselves to be exposed to a drug that has not been proven effective and that may also pose safety risks, subjects generally should not be expected to pay for the drug. In fact, in return for their willingness to be exposed to an unapproved drug, subjects in clinical trials are usually compensated, rather than charged for the drug (71 FR 75168 at 75170, December 14, 2006).

2006, we proposed amending 21 CFR 312.7(d) (71 FR 75168). Although the proposed amendments, if adopted, would expand the circumstances in which charging for an investigational new drug in a clinical trial is appropriate, their purpose and intent are consistent with the policies articulated in the original final rule. Under the proposed amendments, FDA would approve charging for an investigational new drug in a clinical trial only if the charge is necessary to the conduct of the trial. The sponsor would need to demonstrate that the clinical trial could not be conducted unless it could charge for the investigational new drug because the drug's cost is extraordinary (71 FR 75168 at 75180).

### **III. FDA HAS BEEN PROACTIVE AND RESPONSIVE IN FACILITATING AND SUPPORTING RESEARCH, DEVELOPMENT, AND APPROVAL OF PRE-PANDEMIC AND PANDEMIC INFLUENZA VACCINES**

It is an ongoing challenge to develop and maintain sufficient quantities of FDA-approved pre-pandemic and pandemic influenza vaccines. However, recent and ongoing research and regulatory activities indicate that pandemic influenza vaccine development is occurring and expanding. For example, in February 2007, FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened to discuss data in support of a promising pandemic influenza vaccine in development. In April 2007, FDA announced its licensure of this vaccine, the first vaccine in the United States for humans against the avian influenza virus H5N1. The federal government has purchased this licensed vaccine for inclusion within the Strategic National Stockpile. In December 2007, FDA sponsored a public workshop entitled "Immune Correlates of Protection against Influenza A Viruses in Support of Pandemic Vaccine Development." The purpose of the public workshop was to identify the gaps in knowledge and abilities in addressing the unique challenges encountered in the development and evaluation of vaccines against pandemic influenza. In February 2008, FDA's VRBPAC convened to discuss clinical development pathways for influenza vaccines for pre-pandemic and pandemic uses.

Additionally, the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID), is at the forefront of numerous pandemic influenza research activities. In 2006 and 2007, NIAID awarded several grants to academic research institutions and to industry in support of research projects focused on identifying novel influenza therapeutic candidates. NIAID also initiated several clinical trials for promising pandemic influenza vaccines in development. ClinicalTrials.gov, a Web database that provides updated information on federally and privately supported clinical trials, lists several pandemic influenza vaccine trials that have been completed as well as trials that are currently recruiting subjects.

As stated previously, your request fails to provide any evidence that clinical trials for investigational pandemic influenza vaccines could not be conducted but for charging for "Best Efforts." Current ongoing research contradicts your assertion that charging for "Best Efforts" is in fact necessary for the development of pandemic influenza vaccine.

## CONCLUSION

Given the agency's understanding of your request and because FDA does not regulate a sponsor's efforts to obtain financing for the research and development of its products unless such efforts include promotion of an unapproved product, we deny your Petition. To the extent that 21 CFR 312.7 may be applicable, your requested amendments to the regulations could result in the promotion, sale, and commercialization of investigational pre-pandemic and pandemic influenza vaccines before we have determined whether such vaccines are safe, pure, and potent. This would not only contravene FDA's mission and the purpose and intent of the regulations as adopted by the agency, but also could create a potential conflict of interest that jeopardizes the integrity of the clinical trial process. Your requested amendments would permit charging for "Best Efforts" although you have failed to explain why charging is essential. As stated above, ongoing clinical research for the development of a pandemic vaccine has shown that charging for "Best Efforts" is not necessary. Further, granting the Petition could create the appearance that FDA endorses investigational vaccines in Phase I clinical trials, thus undermining public confidence in our role as an impartial regulator and our ability to protect the public health. Therefore, as discussed above, we deny your request for FDA action.

Sincerely yours,



Jeffrey Shuren, M.D., J.D.  
Associate Commissioner for Policy and Planning

cc: Division of Dockets Management  
(HFA-305)