



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

CBER-04-011

VIA FACSIMILE AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Mr. Arthur Berger
Authorized Agent
GlaxoSmithKline Biologics S.A. d/b/a GlaxoSmithKline
2301 Renaissance Blvd (Bldg #510)
P.O. Box 61540
King of Prussia, PA 19406-2772

Re: BLA STN #103239 Engerix-B® [Hepatitis B Vaccine (Recombinant)]
BLA STN #103475 Havrix® [Hepatitis A Vaccine, Inactivated]
BLA STN #103850 Twinrix® [Hepatitis A Inactivated and Hepatitis B
(Recombinant) Vaccine]

Dear Mr. Berger:

The Advertising and Promotional Labeling Branch (APLB) in the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has reviewed a "Summary of Recommendations For Adult Immunization" (MUV304R0) (summary) for Engerix-B® [Hepatitis B Vaccine (Recombinant)], Havrix® [Hepatitis A Vaccine, Inactivated], and Twinrix® [Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine] submitted by GlaxoSmithKline Biologics S.A. (GSK) under cover of Form FDA 2253. The summary contains false or misleading statements regarding the live attenuated influenza vaccine and fails to reveal material facts regarding specific risks associated with the use of Engerix-B, Havrix, and Twinrix, in violation of sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 352(a) and 321(n)).

The summary creates a serious public health concern because it could lead to incorrect administration of the live attenuated influenza vaccine to individuals, including pregnant women with medical conditions and children from 6 months to up to 5 years old, for whom that product has not been demonstrated to be safe and effective. In addition, this summary was distributed during the height of the flu season with false and misleading information regarding the live attenuated influenza vaccine.

Background

According to the FDA-approved professional labeling (PI), Engerix-B is a noninfectious recombinant DNA hepatitis B vaccine that is supplied as a sterile suspension for

intramuscular administration and is indicated for immunization against infection caused by all known subtypes of hepatitis B virus. Engerix-B will not prevent hepatitis caused by other agents, such as hepatitis A, C, and E viruses, or other pathogens known to infect the liver. Immunization is recommended in persons of all ages, especially those who are, or will be, at increased risk of exposure to hepatitis B virus.

Havrix is a noninfectious hepatitis A vaccine that contains a sterile suspension of inactivated virus for intramuscular administration. Havrix is indicated for active immunization of persons 2 years of age or older against disease caused by hepatitis A virus (HAV). Havrix will not prevent hepatitis caused by other agents such as hepatitis B, C, and E viruses, or other pathogens known to infect the liver. Immunization with Havrix is indicated for those people desiring protection against hepatitis A. Primary immunization should be completed at least 2 weeks prior to expected exposure to HAV.

Twinrix is a sterile bivalent vaccine containing the antigenic components used in producing Havrix and Engerix-B. Twinrix is supplied as a sterile suspension for intramuscular administration. Twinrix is indicated for active immunization of persons 18 years of age or older against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus. Twinrix will not prevent hepatitis caused by other agents such as hepatitis C and E viruses, or other pathogens known to infect the liver. Immunization is recommended for all susceptible persons 18 years of age or older who are, or will be, at risk of exposure to both hepatitis A and hepatitis B viruses.

Examples of important risk information found in the PI for these products include:

- In clinical studies, adverse reactions that were reported, including injection site soreness and fatigue for Engerix-B, injection site soreness and headache for Havrix, and injection site soreness, headache, and fatigue for Twinrix.
- Contraindications such as hypersensitivity to any component of the vaccines, including yeast in Engerix-B, neomycin in Havrix, and yeast and neomycin in Twinrix.

False Statements

In your efforts to "re-create" the ACIP recommendations chart, you have presented significant false information on other products addressed by this chart. For example, you have contradicted the ACIP recommendations chart and made false statements regarding the live attenuated influenza vaccine, as follows:

1. A footnote to the ACIP recommendations chart states, "For healthy persons aged 5-49 years without high risk conditions, either the inactivated vaccine or the intranasally administered influenza vaccine...may be given." That recommendation is consistent with the PI for the intranasally administered, live attenuated influenza vaccine (LAIV), which states that LAIV is indicated for use in "...healthy children and adolescents, 5-17 years of age, and healthy adults, 18-49 years of age" and that it "is not indicated for immunization of individuals less than 5 years of age, or 50 years of age and older..."

In contrast, your summary states, in the column entitled "For whom it is

recommended," that influenza vaccine (inactivated and live attenuated influenza vaccine) is recommended for "People 6m – 50yrs of age with medical problems" and "People (>6m of age) working or living with at-risk people."

Thus, your summary falsely represents that the LAIV is indicated for people from 6 months to up to 5 years old and for persons 50 years of age.

2. As stated above, the ACIP recommends the LAIV only for healthy people without high risk conditions.

In contrast, your summary states in the "For whom it is recommended" section that the influenza vaccine (inactivated and live attenuated) is recommended for "Pregnant women who have underlying medical conditions...regardless of the stage of pregnancy."

We acknowledge that another location in the summary, the contraindications column, states, "Do not give live attenuated influenza vaccine (LAIV) to persons >50 years of age, pregnant women..." and also mentions contraindications for other medical conditions. However, this is insufficient to correct the false or misleading representations regarding the persons for whom this vaccine is recommended. In addition, the information on the age range in the contraindications column is false in relation to the LAIV. Specifically, the LAIV is not approved for use in patients greater than *or equal to* 50 years of age and it is not approved for patients less than 5 years of age.

Failure to Reveal Material Facts

The summary specifically identifies Twinrix by name, and includes the proprietary names and logos for Engerix-B, Havrix and Twinrix just underneath the summary, along with their established names: "Hepatitis B Vaccine (Recombinant)," "Hepatitis A Vaccine, Inactivated," and "Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine," respectively. The left-hand column of the summary lists those diseases, Hepatitis A and B, followed by immunization information for each of those diseases in columns labeled: "For whom it is recommended," "Schedule for routine and 'catch-up' administration," and "Contraindications." However, this summary fails to provide any product-specific risk information that is critical to the safe use of these products (e.g., adverse reactions and specific contraindications, such as hypersensitivity to neomycin for Havrix, as described above). Information about these risks is pertinent to the safety and effectiveness of these products and, therefore, must appear in the summary itself along with the claims of safety and effectiveness information. Cf. 21 CFR 202.1(e)(3)(i).

Conclusions and Requested Actions

Your summary misbrands Engerix-B, Havrix, and Twinrix within the meaning of sections 502(a) and 201(n) of the Act (21 U.S.C. 352(a) and 321(n)) because it contains false or misleading statements regarding the live attenuated influenza vaccine and fails to reveal material facts regarding specific risks associated with the use of these products.

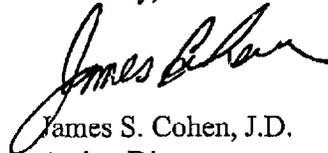
We request that GSK immediately cease the dissemination of violative promotional materials for Engerix-B, Havrix, and Twinrix such as those described above. Please submit a written response to this letter within ten (10) business days of the date of this letter,

stating whether you intend to comply with this request, listing all violative promotional materials for Engerix-B, Havrix, and Twinrix such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, HFM-600, 1401 Rockville Pike, Rockville, Maryland 20852-1448. In all future correspondence regarding this matter, please refer to the BLA/STN number and to CBER-04-011. We remind you that only written communications are considered official responses.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Engerix-B, Havrix, and Twinrix comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,



James S. Cohen, J.D.
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosure