April 4, 2003

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GlaxoSmithKline

GlaxoSmithKline
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Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Response to Federal Register Notice/Request for Information: "Mercury Compounds in Drugs and Food" Docket 98N-1109

Dear Sir/Madam:

Reference is made to our U.S. License No. 1090, providing for the manufacture of the following biological products at GlaxoSmithKline Biologics:

- Engerix-B®-Hepatitis B Vaccine, Recombinant [Reference Number 87-0556, STN 103907]
- Havrix®-Hepatitis A Vaccine, Inactivated [Reference Number 92-0465, STN 103475]
- Infanrix®-Diphtheria and Tetanus Toxoid and Acellular Pertussis Vaccine Adsorbed [Reference Number 95-1773, STN 103647]
- Twinrix®-Hepatitis A Inactivated and Hepatitis B, Recombinant Vaccine [Reference Number 99-0133, STN-103850]
- Pediarix™-Diphtheria and Tetanus Toxoid and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined [Reference Number 99-0800, STN 103907]

Reference is made to the CBER's letter dated July 1, 1999 requesting information regarding the manufacturer's proposal to remove or reduce the content of mercury-containing components in pediatric vaccines and a subsequent CBER letter of May 31, 2000 requesting an update on the progress toward the goal to remove or reduce the content of mercury-containing components in pediatric vaccines. Additional reference is made to GlaxoSmithKline's responses to these letters on July 26, 1999 and July 7, 2000 filed to our US license 1090.

This letter serves as official response to the Federal Register Notice noted above.

98N-1109

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For GlaxoSmithKline, the only licensed pediatric vaccine that contains detectable levels of a mercury containing compound is Engerix-B® (Hepatitis B Vaccine, (Recombinant) [Reference Number 87-0556, STN 103907]. Following the Agency's letter of July 1, 1999 and the statement issued by the American Academy for Pediatrics (AAP) on July 8, 1999 regarding the content of mercury in pediatrics vaccines, GSK immediately implemented plans to significantly reduce thimerosal in the *Engerix-B* vaccine product by omitting thimerosal from the final formulation process and with a later goal of removing thimerosal entirely, i.e. manufacturing the vaccine without use of thimerosal in the purification process.

The following actions have been implemented for *Engerix-B* since our letter of July 7, 2000:

Reduction of thimerosal in *Engerix-B* has been successful upon removal of its use as a preservative during final vaccine formulation.

- Pediatric preservative-free monodose presentation: Supplement 99-1110 was submitted September 10, 1999 to support approval of the pediatric 10 mcg/0.5 ml dose monodose preservative-free presentation. Approval was obtained 28 March 2000.

  This formulation contains no thimerosal added as a preservative, and only a trace amount remains from the manufacturing process (<1 mcg thimerosal per dose).

- Adult preservative-free monodose presentation: Supplement submitted August 3, 2000 for the adult 20 mcg/1.0 ml monodose preservative-free presentation. As with the pediatric presentation described above, this formulation contains no thimerosal added as a preservative, and only a trace amount remains from the manufacturing process (<2 mcg thimerosal per adult dose). Approval was received on December 1, 2000.

Complete removal of thimerosal from the manufacturing process is being investigated.

- Pediatric and adult thimerosal-free, preservative-free formulations: The feasibility of a thimerosal-free, preservative-free product is currently being investigated in clinical studies. The bulk obtained from the thimerosal-free manufacturing process is intended for formulation of combination vaccines that contain the hepatitis B antigen. Depending on the required database for submission of the thimerosal-free supplement, and the effect of this change on multiple combination products, submission of this product for licensure will be planned.

Other Pediatric Vaccine Products:

As noted in our responses of July 26, 1999 and July 7, 2000, our other vaccines approved under License 1090 for pediatric use are free of mercury-containing derivatives (i.e. Havrix® (Hepatitis A Vaccine, Inactivated) [Reference Number 92-0465, STN 103475]) or have no detectable concentrations of mercury/derivatives, i.e. Infanrix® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) [Reference Number 95-1773, STN 103647].

With regards to *Infanrix*, since our response on July 7, 2000, we have gained approval of a supplement for the removal of the thimerosal used in early stages of manufacture of the Pa antigens (in the Pa extraction buffer); sBLA 99-0746, approved on September 29, 2000. This process change allowed for a completely "mercury-free" manufacturing process and therefore this product no longer needs to appear on the "Mercury Compounds in Drugs and Food" list.

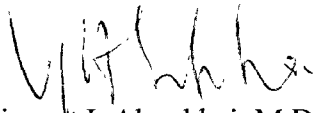
We recently gained approval for our Biologics License Applications for Pediarix™ (Diphtheria and Tetanus Toxoids, Acellular Pertussis Adsorbed, Hepatitis B (Recombinant), and Inactivated Poliovirus Vaccine Combined) [Reference Number 99-0800, STN 103907], which has no detectable levels of mercury or mercury components. This combination vaccine contains Pa antigens manufactured using the currently approved process of *Infanrix* described above and also contains a hepatitis B component, which differs from the currently approved *Engerix-B* pediatric formulation, as it utilizes a cysteine dialysis step in the manufacture of the hepatitis B component which brings the thimerosal content to < 25 ng of thimerosal /20 mcg of HbsAg which by calculation is <12.5 ng per dose.

Non-Pediatric Vaccine Products:

Since our responses of July 26, 1999 and July 7, 2000, we have gained approval for Twinrix® (Hepatitis A inactivated & Hepatitis B recombinant vaccine) [Reference Number 99-0133 and 99-0152 respectively, STN 013850]. *Twinrix* is approved for administration to subjects 18 years of age and above and this combination vaccine contains the currently approved bulk formulation of *Engerix-B* (< 2 mcg thimerosal/1.0 mL dose) and it does not contain thimerosal as a preservative.

Should you have any comments or require an additional information, please do not hesitate to contact me at 610-787-3760.

Sincerely,



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