Date: May 27, 2008

From: Soju Chang, MD, MPH
APPROVED
By Soju Chang at 3:50 pm, May 29, 2008
Medical Officer, Vaccine Safety Branch, Division of Epidemiology

To: Michael J. Schmitt, PhD
Chair, Kinrix™ Biologics License Application Review Committee

Through: Sukhminder K. Sandhu, PhD, MPH
APPROVED
By Sukhminder Kaur Sandhu at 7:00 pm, May 29, 2008
Acting Chief, Vaccine Safety Branch

Robert Ball, MD, MPH, ScM
APPROVED
By Robert Ball MD, MPH, ScM at 9:20 am, May 30, 2008
Acting Director, Division of Epidemiology

Re: Pharmacovigilance Plan for STN 125260/0 [Biologics License Application for Diphtheria and Tetanus Toxoids, Acellular Pertussis and Inactivated Poliovirus Combined Vaccine as a Booster Dose to Children 4-6 years of Age]

Introduction

On April 06, 2007, GlaxoSmithKline (GSK) Biologicals submitted a Biologics License Application for Diphtheria and Tetanus Toxoids, Acellular Pertussis and Inactivated Poliovirus (DTaP-IPV) vaccine [trade name Kinrix™]. The DTaP-IPV candidate vaccine consists of a combination of GSK's Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) vaccine (Infanrix®; STN 103647, approved January 29, 1997) and inactivated poliovirus vaccine (IPV). The IPV component is not licensed as a stand-alone IPV vaccine in US. The DTaP and IPV components are the same as those found in GSK's Pediarix® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined; STN 103907; approved December 13, 2002]. All components of the vaccine have been previously studied and licensed for use. DTaP-IPV will be indicated for active immunization against diphtheria, tetanus, pertussis and poliomyelitis, administered as the 5th dose of DTaP and as the 4th dose of IPV in children 4-6 years of age.

GSK Biologicals markets a combined diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccine, currently approved in 31 countries outside of the US and marketed under the names Infanrix-Polio, Infanrix-IPV, and Infanrix tetra. The vaccine is indicated for primary immunization from the age of 2 months against diphtheria, tetanus, pertussis and poliomyelitis and as a booster dose for children who have previously been immunized with DTP and polio antigens. The formulation is identical to that of the US candidate vaccine, with the exception that the vaccine distributed outside of the US contains ≤2.5µg 2-phenoxyethanol per dose. The total patient exposure can be calculated from the number of doses distributed. From the first launch in August 1996 until 06 August 2006, [redacted] doses were distributed. The primary vaccination schedule consists of three doses in the first year of life and can start from the age of 2 months. Therefore, it can be estimated that the number of patients

exposed is between [redacted] individuals, assuming all doses distributed were administered.

Safety Specification

Important Identified Risks/ Important Potential Risks/Important Missing Information

GSK Biologicals considers adverse events (AEs) of large local swelling reactions and stroke as safety aspects of interest. At this stage, based on available data, both from clinical development and from post-marketing surveillance, the company does not consider the above mentioned AEs to be potential risks associated with the candidate DTaP-IPV vaccine. Nevertheless, in further compliance with the applicable guidance, GSK Biologicals will continue to monitor these safety aspects.

Non-clinical

No non-clinical studies were conducted in support of this application. The antigens included in the candidate DTaP-IPV vaccine are well-characterized and have been used for many years as components of other US-licensed vaccines.

Clinical

Limitations of the human safety database

Three pre-licensure clinical studies involved a total of 3,537 children 4 to 6 years of age vaccinated with DTaP-IPV: one pivotal, lot-to-lot consistency study (n=3,156) and one supportive study (n=200) in US; one supportive study (n=181) in Australia. In these clinical trials, safety was evaluated among DTaP-IPV recipients as compared to those who received separate, concomitant administration of Infanrix® and Sanofi pasteur's IPOL® (DTaP+IPV). All subjects received concomitant measles mumps and rubella (MMR) vaccine. Solicited local (e.g., pain, redness, swelling including extensive limb swelling) and systemic (fever, drowsiness, loss of appetite) AEs as well as unsolicited AEs were evaluated.

Populations not studied in the pre-approval phase

The candidate vaccine has not been studied in immunosuppressed individuals or those with chronic diseases during the pre-authorization phase. According to current Advisory Committee on Immunization Practices (ACIP) recommendations, vaccines that include only *inactivated* virus, such as DTaP-IPV, may be safely used in these circumstances; however, the effectiveness might be suboptimal. The use of the candidate vaccine has not been studied in children whose age is outside of the intended age range for the vaccine (i.e., children younger than 4 or older than 6 years of age).

Adverse events (AEs)/adverse drug reactions (ADRs)

Regarding solicited local AEs, in the pivotal study, based on two-sided Fisher's exact test, differences between the pooled DTaP-IPV and DTaP+IPV control groups were noted as follows: 1) The percentage of subjects reporting Grade 3 pain at any injection site was greater in the pooled DTaP-IPV group than in the DTaP + IPV control group (1.6% *vs* 0.7%; $p<0.05$); 2) The percentages of subjects reporting any or Grade 3 pain at the DTaP-based injection site, was greater in the pooled DTaP-IPV groups (57.0% and 1.6%, respectively) than in the DTaP + IPV control group (53.3% and 0.6%, respectively; $p<0.05$ for both comparisons); 3) The percentage of subjects reporting redness ≥110mm diameter at any injection site, or any redness at the *MMRII* injection site, was greater in the DTaP + IPV control group (4.2% and 9.6%, respectively) than in the DTaP-IPV group (2.9% and 7.2%, respectively; $p<0.05$ for both comparisons). There were no statistically significant differences between the DTaP-IPV pooled group and the control group in terms of the percentages of subjects who sought medical advice for any local solicited AE.

In the US supportive study, no significant differences ($p <0.05$) were observed between groups in the incidence or intensity of solicited local symptoms. Large injection site swelling reactions were defined for both studies as any local swelling with diameter greater than 50mm, any increase in mid upper arm circumference greater than 30mm, or any diffuse swelling preventing or interfering with everyday activities such as writing, drawing, playing, eating, school or daycare attendance, or sleeping. The proportions of subjects reporting large injection site swelling reactions were similar between the pooled DTaP-IPV groups and the DTaP + IPV group in the pivotal study. No comparative statement was made for US supportive study. The Australian supportive study showed that a similar incidence of large swelling reactions was observed after DTaP-IPV or DTaP+IPV booster vaccination. There was no difference between the two groups in incidence and intensity of solicited symptoms occurring after vaccination.

For both US studies, the proportions of subjects reporting solicited general AEs was generally comparable between the pooled DTaP-IPV group and DTaP + IPV control group. There was a significantly greater percentage of subjects reporting fever >38°C in the DTaP-IPV group than in the DTaP + IPV control group. Because there were no statistically significant differences in the proportions of subjects with fever >38.5°C or in the proportion of subjects seeking medical advice for fever or any other solicited general AEs, the difference at the lower temperature range was not considered clinically relevant. There were no apparent differences between groups in the reporting of MMR-specific general symptoms.

No clinically relevant differences between treatment and control groups were detected with regard to reporting of specific unsolicited AEs in either US study. There were no deaths reported. None of the serious AEs (e.g., hypernatremia and dehydration, gastroenteritis and dehydration, asthma, pneumonia) were considered by the investigators to be related to study vaccination. In the US pivotal study, 12 serious AEs (4 with unresolved and 8 with resolved outcomes) in the DTaP-IPV group (n=3,156) and 4 serious (all with resolved outcomes) in the DTaP + IPV control group (n=1,053) were

reported during the entire study period. The four serious AEs with unresolved outcomes included: a 4-year old female with family history of thrombotic events developed cerebrovascular accident (CVA) 30 days after vaccination; a 4-year old male developed necrotizing pneumonia 172 days after vaccination; a 4-year old male developed optic atrophy 180 days after vaccination; and a 5-year old male developed Burkitt's lymphoma 155 days after vaccination. In the US supportive study, 3 serious AEs (all with resolved outcomes) in the DTaP-IPV group (n=200) and 2 serious (all with resolved outcomes) in the DTaP + IPV control group (n=200) were reported during the entire study period. In the Australian supportive study, no serious AEs were reported following the booster dose of DTaP-IPV (n=181).

In response to CBER's request following review of GSK's pre-BLA meeting briefing document, the company prepared a Biologicals Clinical Safety and Pharmacovigilance summary of events medically consistent with stroke, hypercoagulable states, or thrombotic events collected through postmarketing pharmacovigilance activities for DTaP-IPV, *Infanrix*, and *Pediarix* vaccines. Cases were initially identified by searching GSK's worldwide clinical safety database for MedDRA Preferred Terms likely to be associated with CVA, thrombosis or hypercoagulable states. This was followed by medical review of case summaries associated with these terms for selection of cases whose clinical features were consistent with the diagnostic criteria for stroke, thrombosis, thromboembolism, or hypercoagulable states. Finally, cases consistent with the diagnostic criteria for these events were assessed for possible relationship to vaccination with DTaP-IPV, *Infanrix*, or *Pediarix*, considering the following criteria: the time to onset of the event relative to vaccination and possible causes other than vaccination such as an alternative diagnosis, concurrent disease, or concurrent drug. The analysis included all events reported to GSK as of 1 January 2007. It was concluded that the available data do not support an association between vaccination with the candidate DTaP-IPV, *Pediarix*, or *Infanrix* and cerebrovascular accident, thrombosis, thromboembolism, or hypercoagulable states.

At CBER's request, DTaP-IPV pharmacovigilance plan (PVP) was revised to include additional AEs of interest: drug administration errors, febrile seizures, brachial neuritis, arthritis, anaphylaxis, erythema multiforme, encephalopathy, epilepsy, demyelinating disorders of the central nervous system (i.e., optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis), and Guillain-Barré syndrome. The MedDRA preferred term "Drug administration error" was listed as one of the top 10 most frequently reported AEs for DTaP-IPV vaccine in the GSK's post-marketing database. There were 52 reports coded with "Drug administration error" and all were non-serious. The most frequently reported types of drug administration errors were administration of DTaP-IPV instead of DTaP-IPV/Haemophillus influenzae type b (n = 14; 26 %), administration of an extra dose of DTaP-IPV (n=10; 19%), and DTaP-IPV mixed with other vaccine in the same syringe (n=6; 12%). Of the 52 reports, 11 (21%) described adverse events following immunization. The most common adverse events reported were injection site reactions and pyrexia, both of which are listed in the proposed DTaP-IPV prescribing information.

Identified and potential interactions, including food-drug and drug-drug interactions

Co-administration of DTaP-IPV vaccine with other vaccines has not been studied with the exception of MMR vaccine. Co-administration of MMR with DTaP-IPV, compared to co-administration with DTaP + IPV, did not produce any clinically-important differences in the safety profiles of either vaccine. As previously discussed with the agency, post-marketing studies will include evaluation of co-administration of the DTaP-IPV candidate vaccine with varicella vaccine. In patients receiving immunosuppressive therapy or patients with immunodeficiency an adequate immunologic response may not be achieved.

Epidemiology

In USA, the incidences of these vaccine-preventable diseases (polio, diphtheria, tetanus and pertussis) have dramatically declined in the past few decades, in particular among children under 5 years of age. Regarding the epidemiology of potential safety risks, a study shows that entire proximal limb swelling occurs in 2% to 6% of children given booster doses of DTaP vaccines. The annual incidence of stroke in US children less than 15 years of age is between 2.3 and 6.4 (95% CI: 2.5, 10.4) per 100,000.

Pharmacological class effects

Large local injection site reactions: large local injection site reactions have been documented with successive doses of DTaP vaccines with the highest rates reported after the 4th and 5th consecutive doses. A review of several clinical studies showed that entire proximal limb swelling occurs in 2% to 6% of children given booster doses of DTaP vaccines. Also, it is reported in medical literature that swelling reactions generally lasted a few days and resolved without sequelae.

Febrile seizure: findings from a literature review by GSK for febrile seizures showed that febrile seizures might be seen in 3% - 4% of young children. Studies showed an increased risk of febrile seizures after diphtheria tetanus whole cell pertussis vaccine, but the risk of febrile seizures was significantly lower after acellular pertussis vaccine. Data from clinical trials and a large, post-marketing observational study indicated that the risk of febrile seizure after acellular pertussis vaccine was approximately 1 per 20,000 vaccinations.

Brachial neuritis: GSK reviewed the English-language, indexed medical literature published after the issuance of the 1994 Institute of Medicine (IOM) report on AEs associated with childhood vaccines. GSK did not identify any controlled studies of brachial neuritis after vaccination with tetanus toxoid or tetanus toxoid-containing vaccines. The Immunization Safety Review Committee of IOM stated in the 1994 IOM report that the evidences, based on case reports or uncontrolled observational studies, favored acceptance of a causal relation between tetanus toxoid and brachial neuritis.

Arthritis: the IOM noted that the biological plausibility for a causal relationship between diphtheria and tetanus toxoids and arthritis is based on "the toxoid's potential to induce serum sickness," and concluded that the evidence was inadequate to accept or reject a causal relationship. A review by GSK of the English-language, indexed medical literature published after the IOM report was issued did not identify any controlled studies of arthritis after vaccination with tetanus toxoid or tetanus toxoid-containing vaccines.

Anaphylaxis: in 1994, the IOM concluded that the available evidence established a causal relationship between tetanus toxoid and tetanus toxoid-containing vaccines and anaphylaxis. A study of anaphylaxis in children and adolescents using vaccine safety datalink (VSD) databases identified 5 potentially vaccine-related cases of anaphylaxis after the administration of over 7.6 millions vaccine doses during the period 1991-1997, yielding a risk of 0.65 cases/million vaccine doses (95% CI: 0.21, 1.53). Anaphylactic reactions are labeled (expected) events for GSK's DTaP vaccine, and are therefore labeled for DTaP-IPV vaccine.

Erythema multiforme: the IOM concluded that there is biological plausibility for a "relation between diphtheria and tetanus toxoids and erythema multiforme on the basis of a hypersensitivity mechanism and an investigation of bacterial injection in one human subject," but judged the evidence to be inadequate to accept or reject a causal relationship between either diphtheria or tetanus toxoid and erythema multiforme. A review by GSK of the English-language, indexed medical literature published after the IOM report was issued did not identify any controlled studies of erythema multiforme after vaccination with tetanus toxoid or tetanus toxoid-containing vaccines.

Encephalopathy: in 1991, the IOM concluded that the evidence is consistent with a causal relation between tetanus, diphtheria and whole cell pertussis vaccine and acute encephalopathy, defined in the controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis. Later, the 1994 IOM report stated that the evidence favored rejection of a causal association between tetanus toxoid-containing vaccines and encephalopathy. Subsequent studies have supported this lack of a causal association. During 1993-2002, active surveillance in Canada failed to ascertain any acute encephalopathy cases causally related to whole-cell or acellular pertussis vaccines among a population administered 6.5 million doses of pertussis-containing vaccines. In the US, a case-control study of children hospitalized with encephalopathy or related conditions, which was nested in a cohort of more than 2 million children, did not demonstrate an increased risk of encephalopathy in the 90 days following vaccination with whole-cell pertussis vaccine.

Epilepsy (residual seizure disorder other than infantile spasms): approximately 0.5 to 2 percent of the population experiences epilepsy. The IOM report concluded that the evidence available in 1994 was inadequate to accept or reject a causal relationship between either tetanus toxoid alone or tetanus and diphtheria toxoids and epilepsy. Subsequent to the IOM report, studies showed no increased risk of afebrile seizures after whole-cell pertussis. A retrospective cohort analysis that demonstrated a nearly six-fold

increase in the risk of febrile seizures after whole-cell pertussis vaccine did not show an increased risk of afebrile seizures during 637,989 person-years of observation after 340,386 DTP vaccinations. Convulsion is an expected (labeled) event for *Infanrix*, and, therefore, would be expected for DTaP-IPV. Epilepsy is unexpected for DTaP-IPV, per the proposed US prescribing information.

Demyelinating diseases of the central nervous system (optic neuritis, transverse myelitis, acute disseminated encephalomyelitis): the IOM concluded that there is biological plausibility for a causal relationship between vaccines and demyelinating diseases of the central nervous system (CNS), but that the available evidence was inadequate to accept or reject a causal relationship between tetanus toxoid-containing vaccines and demyelinating diseases of the CNS. A subsequent case-control study of CNS demyelinating diseases in adults, using the VSD databases, did not demonstrate an increased risk of multiple sclerosis or optic neuritis with tetanus vaccination. Another supportive study showed no increased risk of exacerbation of multiple sclerosis within 2 months of vaccination with tetanus toxoid.

Guillain-Barré syndrome: based primarily on a single, well-documented case report, the IOM concluded that evidence favored acceptance of a causal relation between tetanus toxoid-containing vaccines and Guillain-Barré syndrome. A subsequent analysis by the Centers for Disease Control and Prevention (CDC) of active surveillance data from 2 large, population-based studies failed to demonstrate an association between receipt of a tetanus toxoid-containing vaccine and onset of Guillain-Barré syndrome within 6 weeks following vaccination; in these studies, adult and child populations received an estimated 0.7 million to 1.2 million and 8.1 million doses, respectively, of tetanus-toxoid-containing vaccine, and the number of cases of Guillain-Barré syndrome observed after administration of such vaccines in both adults and children was less than the number expected by chance alone. The CDC researchers concluded that, if an association between Guillain-Barré syndrome and tetanus toxoid-containing vaccines exists, it must be extremely rare and not of public health significance.

Summary

The company concludes that currently available safety and efficacy data from the clinical trials conducted with candidate DTaP-IPV vaccine do not indicate any safety risks. The information that can be defined according to applicable guidance as missing or incomplete at this stage in the life-cycle of the candidate DTaP-IPV vaccine relates to the populations not thoroughly investigated in the pre-authorization phase – immunocompromised children, and children with chronic diseases. However, according to current recommendations, the candidate vaccine may be safely used in these circumstances.

Action Plan for Safety Issues/ Summary of Actions to Be Completed, Including Milestones

To establish enhanced passive surveillance consisting of closely monitoring all worldwide spontaneous reports of large injections site swelling reactions, stroke/ thrombus/thromboembolisms/hypercoagulable states, febrile seizure, arthritis, brachial neuritis, anaphylaxis, erythema multiforme, epilepsy, and Guillain-Barré syndrome. The objective is to obtain as much follow-up information as possible for the above AEs. Efforts will include use of questionnaires to obtain a standardized and detailed description of the cases. GSK will perform routine pharmacovigilance for the demyelinating diseases of the central nervous system (optic neuritis, transverse myelitis, acute disseminated encephalomyelitis). Additional milestones for evaluation and reporting for described AEs will be agreed upon with the Agency.

Comments

- Please note that GSK will conduct an enhanced passive surveillance for large injections site swelling reactions, stroke/thrombus/thromboembolisms/ hypercoagulable states, febrile seizure, arthritis, brachial neuritis, anaphylaxis, erythema multiforme, epilepsy, and Guillain-Barré syndrome and perform routine pharmacovigilance for the demyelinating diseases of the central nervous system (optic neuritis, transverse myelitis, acute disseminated encephalomyelitis).
- Pursuant to 21 CFR 600.80(c)(2), please provide the contractor for VAERS periodic reports of large injection site swelling reactions, febrile seizure, arthritis, brachial neuritis, anaphylaxis, erythema multiforme, epilepsy, and Guillain-Barré syndrome from within the US (all reported events) and from around the world (those reported as serious events). In addition, please expedite all (15-day) reports for stroke/thrombus/ thromboembolism/hypercoagulable states and demyelinating diseases of the central nervous system (optic neuritis, transverse myelitis, acute disseminated encephalomyelitis).