**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Biologics Evaluation and Research**

# MEMORANDUM

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| To: | Craig Zinderman, MD, MPH<br>Associate Director for Medical Policy<br>Office of Biostatistics and Epidemiology (OBE)<br>Center for Biologics Evaluation and Research (CBER) |
| Through: | Meghna Alimchandani, MD<br>Deputy Director, Division of Epidemiology (DE), OBE, CBER |
| From: | Wenyu Sun, MD, MPH<br>Medical Officer, Pharmacovigilance Branch, DE, OBE, CBER |
| Subject: | Safety and Utilization Review for the Pediatric Advisory Committee |
| Applicant: | GlaxoSmithKline Biologicals (GSK) |
| Product: | Hiberix [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] |
| STN: | 125347/376 |
| Indication: | Hiberix is indicated for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* (*H. influenzae*) type b. Hiberix is approved for use in children aged 6 weeks through 4 years. |
| Meeting Date: | Pediatric Advisory Committee Meeting, September 2020 |

## Contents

# 1 INTRODUCTION

## *1.1 Objective*

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of BLA supplement 125347/231 on January 14, 2016 for the use of Hiberix for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b in children 6 weeks to 14 months of age.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

## *1.2 Product Description*

Hiberix is indicated for active immunization for the prevention of invasive disease caused by Haemophilus influenzae (H. influenzae) type b. Hiberix is approved for use in children aged 6 weeks through 4 years (prior to fifth birthday).[1]

Hiberix contains 10 µg Haemophilus b capsular polysaccharide covalently bound to Tetanus Toxoid (TT), per 0.5 mL dose. Hiberix is supplied as a sterile, lyophilized powder which is reconstituted with the accompanying saline diluent at the time of use for intramuscular injection. Hiberix contains no preservative or adjuvant.

## *1.3 Regulatory History*

- 1996: Hiberix first licensed in Germany. Since then, it has been licensed in more than 100 countries worldwide.
- August 19, 2009: FDA initial approval of STN 125347/0 for use as a booster dose in children 15 months to 4 years of age, under accelerated approval regulations.
    - This approval triggered a 2011 presentation to the PAC for the review period August 19, 2009 – August 18, 2010.
- January 14, 2016: FDA approval of STN 125347/231 for use in children 6 weeks to 14 months of age
    - This approval is the trigger for the presentation to the 2020 PAC with review period January 14, 2016 – February 29, 2020
- April 30, 2018: FDA approval of STN 125347/309 to include safety and effectiveness data and describe the clinical benefit of Hiberix administered as a booster dose. [Note: Approval of this supplement (STN 125347/309) fulfilled the accelerated

[1] Hiberix U.S. package insert; updated May 8, 2019

approval required study listed in initial approval letter (STN 125347/0).]

## 2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
    - VAERS reports for Hiberix during January 14, 2016 to February 29, 2020
- Manufacturer's Submissions
    - Hiberix U.S. package insert; updated May 8, 2019
    - Applicant response to information request regarding dose distribution data, received April 30, 2020
    - Pharmacovigilance Plan, dated February 2015
    - Periodic safety reports
- FDA Documents
    - STN 125347/231 Hiberix Approval Letter, dated January 14, 2016
    - STN 125347/231 OBE/DE Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

## 3 LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

## 4 PRODUCT UTILIZATION DATA

GSK provided distribution data for the US and worldwide for time intervals January 1, 2016 to February 29, 2020:

- U.S.: 3,677,000 doses
- Worldwide (outside U.S.): 1,065,000 doses

GSK does not have data directly indicating the number of doses in pediatrics versus adults. However, GSK believes that it is reasonable to assume that essentially all doses were administered to pediatric population because the labelled indication in the U.S. is for use in individuals 6 weeks through 4 years of age. Note that the number of doses distributed is an estimate of the number of patients vaccinated because doses may have been distributed without being administered to patients or patients may have received more than one dose.

# 5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

## *5.1 Pharmacovigilance Plan*

The manufacturer's current Pharmacovigilance Plan (PVP), dated February 2015, lists the following important identified risks and missing information (see Table 1); there are no important potential risks for Hiberix.

**Table 1: Hiberix Safety Concerns**

| **Important Identified Risks** |
|---|
| Hypersensitivity and allergic reactions |
| Angioedema |
| Hypotonic-hyporesponsive episode |
| Convulsion (with or without fever) |
| Syncope |
| Somnolence |
| Apnea |
| Urticaria |
| Rash |
| Extensive limb swelling |
| Injection-site induration |
| **Important Potential Risks** |
| None |
| **Missing Information** |
| Immunocompromised children |
| Children with chronic diseases |

Syncope is a commonly occurring event in response to pain, fear or emotional distress triggered by injection. A review of syncope after vaccination revealed that 63% of syncopal episodes occurred within 5 minutes after vaccination and 89% occurred within 15 minutes of vaccine administration.[2] Hypotonic-hyporesponsive episodes (HHE) is defined as an event of sudden onset occurring within 48 hours of immunization, with duration of the episode ranging from 1 minute to 48 hours, in children younger than 10 years of age.[3]. HHE has been observed after vaccination with acellular pertussis and other nonpertussis-containing vaccines. Convulsions occur more commonly in subjects with fever because elevated temperature leads to neurological dysfunction. Apnea commonly occurs in premature infants due to immaturity of the neurological and

[2] Braun MM, Patriarca PA, Ellenberg SS. Syncope after immunization. Arch Pediatr Adolesc Med 1997;151:255--9.
[3] Braun MM, Terracciano G, Salive ME, Blumberg DA, Vermeer-de Bondt PE, Heijbel H, Evans G, Patriarca PA, Ellenberg SS. Report of a US Public Health Service workshop on hypotonic-hyporesponsive episode (HHE)after pertussis immunization. Pediatrics 1998; 102(5):e52; PMID:9794982; https://doi.org/10.1542/peds.102.5.e52

respiratory system in premature infants. All important identified risks are included in section 6.2 *Postmarketing Experience* of the package insert. In addition, syncope, apnea in premature infants, and preventing/managing allergic reaction are listed in section 5 *Warnings and Precautions* of the package insert.
Regarding missing information in immunocompromised children and children with chronic diseases, the sponsor points out that Hiberix may safely be used in these populations according to CDC guidance[4].

The identified risks listed in Table 1 are common to this product class and will be monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no open postmarketing studies for Hiberix (please see section 5.2). The applicant fulfilled pediatric study requirement for all relevant pediatric age groups. There are no postmarketing requirement (PMR) safety-related studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for Hiberix.

### *5.2 Postmarketing Studies*

Required pediatric study under the Pediatric Research Equity Act (PREA):
The applicant fulfilled pediatric study requirements for all relevant pediatric age groups. Hiberix is approved in persons 6 weeks through 4 years of age.

## 6 ADVERSE EVENT REVIEW

### *6.1 Methods*

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Hiberix between January 14, 2016 to February 29, 2020. VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the vaccine.

[4] US Centers for Disease Prevention and Control. Recommended adult immunization schedule - United States, October 2006 - September 2007. MMWR 2006;55(40):Q1-Q4.

### *6.2 Results*

The results of the VAERS search of AE reports for Hiberix during the PAC review period are listed in Table 2 below. There were 304 US reports and 135 foreign reports for review period January 14, 2016 to February 29, 2020.

**Table 2: Hiberix VAERS reports during January 14, 2016 – February 29, 2020**

| Age | Serious Non-Fatal* | | Deaths | | Non-Serious | | Total Reported | |
|---|---|---|---|---|---|---|---|---|
| | US | Foreign | US | Foreign | US | Foreign | US | Foreign |
| **<18 years** | 42 | 60 | 9 | 1 | 240 | 1 | 291 | 62 |
| **≥ 18 years** | 0 | 8 | 0 | 0 | 7 | 0 | 7 | 8 |
| **Unknown** | 1 | 61 | 0 | 4* | 5 | 0 | 6 | 65 |
| **All Ages** | 43 | 129 | 9 | 5 | 252 | 1 | 304 | 135 |

** Review of the case narratives indicated these were pediatric deaths*.
Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability, and otherwise medically important conditions (OMIC).

#### 6.2.1 Deaths

There were 14 pediatric deaths reported during the review period, of which 9 were US reports and 5 were foreign reports. (Note: Based on review of case narratives, the 4 foreign deaths with "unknown age" in Table 2 were determined to involve pediatric patients.) There were no adult deaths. All death reports were individually reviewed, and narratives are summarized below:

U.S. pediatric death reports:

1. A 3-month-old female who received Pediarix, Hiberix, Rotateq and Prevnar13 died (b) (6) days after the vaccinations. Her autopsy reported that the final cause of death was "respiratory insufficiency secondary to early bronchopneumonia and chronic interstitial pneumonitis. The findings grossly are also consistent with Sudden infant Death Syndrome (SIDS)".

2. A 2-month-old male who received Pediarix, Hiberix, Rotateq, and Prevnar13 died (b) (6) after the vaccinations. His autopsy reported that the cause of death was "undetermined."

3. A 2-month-old male who received Pediarix, Hiberix, Rotateq, and Prevnar13 died (b) (6) days after the vaccinations. His autopsy reported that the cause of death was sudden unexpected death in infancy.

4. A 7-month-old female who received Pediarix, Engerix-B, Hiberix, Rotarix, and Prevnar13 died (b) (6) days after the vaccinations. Her autopsy reported that the cause of death was sudden unexplained infant death (SUID).

5. A 1-month-old male who received Infanrix, Hiberix, Rotateq, Prevnar13, and Ipol died (b) (6) after the vaccinations. His autopsy reported the cause of death as "undetermined".

6. A 3-month-old male who were born prematurely with low birth weight, heart murmur and cleft palate died (b) (6) days after receiving Hiberix. The cause of death was unknown.

7. An 11-month-old female who received Infanrix, Engerix-B, Hiberix, Ipol, and Afluria QIV experienced complex febrile seizures on the same day of vaccination. (b) (6) later, she died of asphyxia complicating hydroxyzine toxicity according to the autopsy report.

8. A 16-month-old male who received Infanrix, Flulaval QIV, Hiberix, and Prevnar13 died (b) (6) days after the vaccinations. His autopsy reported that the cause of death was "undetermined".

9. A 6-month-old female who received Pediarix, Hiberix, Rotateq, and Prevnar13 died (b) (6) after vaccination. Her autopsy reported the cause of death as "undetermined".

Foreign pediatric death reports:

10. A 15-month-old male in New Zealand who received Hiberix, MMR II, and Prevnar13 for prophylaxis died (b) (6) days after the vaccination. The cause of death was unclear, and it was unclear whether an autopsy was performed.

11. A child (gender not reported, up to 59-month-old) who received an unspecified DTP vaccine, unspecified oral polio vaccine, unspecified haemophilus influenzae vaccine, unspecified hepatitis vaccine, unspecified measles vaccine, and BCG vaccine died after an unspecified period following the vaccination. Streptococcus pneumoniae was isolated from a blood culture taken on admission. The cause of death was not specified.

12. A young infant (gender and exact age not reported) in the United Kingdom who

received DTP, Haemophilus influenza vaccine, meningococcal C vaccine, and oral polio vaccine died (b) (6) after the vaccination. The autopsy reported that the cause of death was hematophagic histiocytosis.

13. A 5-year-old male with history of congenital asplenia, atrioventricular septal defect, double outlet of right ventricle, and total anomalous pulmonary venous connection who received unspecified Haemophilus influenzae type b vaccine for prophylaxis died after an unspecified period following the vaccination. The laboratory investigation revealed pneumococcal bacteremia.

14. A male child (age not reported) who previously received Synflorix and Haemophilus influenzae vaccine died of Hemophilus infection.

*Reviewer comments*: There were no reports of pediatric deaths that were attributed to Hiberix based on FDA medical review of the cases. Alternate causes of death were provided in some cases (as documented in above narratives), while limited clinical information in other cases precluded further assessments. Some cases were attributed to Sudden infant death syndrome [SIDS], which is common in this age group, Approximately 3500 infants die annually in the United States from sleep-related infant deaths, including sudden infant death syndrome (SIDS), ill-defined deaths, and accidental suffocation and strangulation in bed.[5] Sudden unexpected infant death (SUID), also known as sudden unexpected death in infancy (SUDI), is a term used to describe any sudden and unexpected death, whether explained or unexplained (including sudden infant death syndrome [SIDS] and ill-defined deaths), occurring during infancy. SIDS is the sudden unexpected death of an apparently healthy infant younger than age 12 months whose cause of death remains unknown despite a death scene investigation, a review of the clinical history, and an autopsy.[6] SIDS remains one of the leading causes of infant death in the United States. It is reported that the US SIDS rate was 40 deaths per 100,000 live births in 2013.[7] The Institute of Medicine has reviewed the topic of SIDS and concluded, "The evidence favors rejection of a causal relationship between exposure to multiple vaccines and SIDS." [8]

[5] Moon RY; TASK FORCE ON SUDDEN INFANT DEATH SYNDROME. SIDS and Other Sleep-Related Infant Deaths: Evidence Base for 2016 Updated Recommendations for a Safe Infant Sleeping Environment.
[6] Goldberg N, Rodriguez-Prado Y, Tillery R, Chua C. Sudden Infant Death Syndrome: A Review. Pediatr Ann. 2018 Mar 1;47(3):e118-e123.
[7] Moon RY; TASK FORCE ON SUDDEN INFANT DEATH SYNDROME. SIDS and Other Sleep-Related Infant Deaths: Evidence Base for 2016 Updated Recommendations for a Safe Infant Sleeping Environment
[8] Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy. Stratton KR, Almario DA, Wizemann TM, and McCormick MC (eds). Washington, DC: National Academy Press, 2003

### 6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 172 serious non-fatal reports, including 102 pediatric reports and 8 adult reports. Age was unknown for the remaining 62 reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for pediatric patients are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

**Table 3: Most frequently reported PTs for serious non-fatal pediatric reports (<18years)**

| Preferred Term (PT) | Number of Serious Reports | Label* Status |
|---|---|---|
| Pyrexia | 50 | Labeled (Fever labeled under 6.1 *Clinical Trials Experience*) |
| Vomiting | 22 | Labeled (6.1 *Clinical Trials Experience*) |
| Irritability | 15 | Labeled (6.1 *Clinical Trials Experience*) |
| Crying | 14 | Labeled (Pain/Irritability are labeled under 6.1 Clinical Trials Experience. "Grade 3 irritability defined as crying that could not be comforted/prevented normal activity") |
| Diarrhoea | 14 | Labeled (6.1 *Clinical Trials Experience*) |
| Febrile convulsion | 12 | Labeled (6.2 *Postmarketing Experience*) |
| Hypophagia | 11 | Labeled (*Loss of appetite* labeled under 6.1 *Clinical Trials Experience*) |
| Decreased appetite | 10 | Labeled (*Loss of appetite* labeled under 6.1 *Clinical Trials Experience*) |
| Intussusception | 10 | Unlabeled |
| Lethargy | 10 | Unlabeled |
| Cyanosis | 9 | Labeled (6.2 *Postmarketing Experience*) |
| Seizure | 9 | Labeled (6.1 *Clinical Trials Experience*) |
| Hypotonia | 8 | Labeled (6.2 *Postmarketing Experience*) |
| Pallor | 8 | Labeled (6.2 *Postmarketing Experience*) |
| Tremor | 8 | Unlabeled |
| Cough | 8 | Unlabeled |
| Abnormal behaviour | 7 | Unlabeled |
| Dehydration | 7 | Unlabeled |
| Urine output decreased | 7 | Unlabeled |
| Anxiety | 7 | Unlabeled |
| Enema administration | 6 | Not applicable |
| Dyspnoea | 6 | Unlabeled |
| Tachycardia | 6 | Unlabeled |

*Label dated May 8, 2019

Note: PTs occurring with a frequency >5 reports are shown in above table.

The most frequently reported PTs in non-fatal serious pediatric reports are either labeled events or consistent with an already labeled event. *Intussusception* is an adverse event included in the package insert of rotavirus vaccine usually administered concomitantly with Hiberix as part of the recommended immunization schedule. *Lethargy* may be related to labeled events for *Drowsiness* (6.1 *Clinical Trials Experience)* and *Somnolence* (6.2 *Postmarketing Experience). Tremor* may be related

to labeled events for *Convulsion* and *Seizure* (6.1 *Clinical Trials Experience).* *Dehydration* and *Urine output decreased* may be related to labeled events for *Vomiting* and *Diarrhea* (6.1 Clinical Trials Experience). Dyspnea may be related to labeled events for Pain/Irritability (6.1 Clinical Trials Experience). Other unlabeled PTs (*Cough, Anxiety, Tachycardia, Abnormal behaviour*) are non-specific events that may be related to multiple conditions. *Enema administration* (procedure) is not an AE. Additionally, we reviewed the most frequent PTs for the 62 reports submitted for patients of unknown age. The reports in this group are likely pediatric (since Hiberix is approved in children 6 weeks through 4 years of age in the U.S., and overall there were very few reports in adults); and almost all of the unknown age reports were foreign. The events in this group included the PTs seen in other pediatric reports, as well as two additional labeled events for *Hypotonic-hyporesponsive episode* (6.2 *Postmarketing Experience*) and *Injection site reaction* (6.1 *Clinical Trials Experience* includes "Local reactions at the injection site").

The most frequently reported PTs for 8 adult serious non-fatal cases included either labeled events or consistent with an already labeled event: *Pyrexia* (N=4) [Fever labeled under 6.1 *Clinical Trials Experience*], and *Skin lesion* (N=2) [injection site *induration* labeled under 6.2 *Postmarketing Experience*]. Other unlabeled PTs, *Malaise* (N=2) and *Nausea* (N=2), are non-specific events.

### 6.2.3 Non-serious Reports

During the reporting period, there were 253 non-serious reports; 241 of which involved pediatric patients. The 10 most frequently reported PTs for pediatric patients are displayed in Table 4. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

**Table 4: Ten most frequently reported PTs for non-serious pediatric reports (<18years)**

| Preferred Term (PT) | Number of Non-Serious Reports | Label* Status |
|---|---|---|
| Pyrexia | 59 | Labeled (Fever labeled under 6.1 *Clinical Trials Experience*) |
| Irritability | 28 | Labeled (6.1 *Clinical Trials Experience*) |
| Injection site erythema | 26 | Labeled (Local reactions at injection site include Redness, 6.1 *Clinical Trials Experience*) |
| Rash | 25 | Labeled (6.2 *Postmarketing Experience)* |
| Injection site swelling | 23 | Labeled (Local reactions at injection site include Swelling, 6.1 *Clinical Trials Experience*) |
| Urticaria | 20 | Labeled (6.2 *Postmarketing Experience)* |
| Injection site discolouration | 19 | Unlabeled |

| Preferred Term (PT) | Number of Non-Serious Reports | Label* Status |
|---|---|---|
| Crying | 18 | Labeled (Pain/Irritability are labeled under 6.1 Clinical Trials Experience. “Grade 3 irritability defined as crying that could not be comforted/prevented normal activity”) |
| No adverse event | 14 | Not applicable |
| Erythema | 11 | Labeled (Local reactions at injection site include redness) |
| Rash generalised | 11 | Labeled (Rash labeled under 6.2 *Postmarketing Experience)* |
| Screaming | 11 | Unlabeled |

*Label dated May 8, 2019

Most reported PTs are labeled events or consistent with an already labeled event. *Screaming* may be related to labeled events for *Irritability, Fussiness, Restlessness* (6.1 *Clinical Trials Experience*). *Injection site discoloration* is further discussion in section 6.3 Data mining.

There were 7 U.S. non-serious reports in adults. Most common PTs for adult non-serious reports included: *Injection site pain* and *Injection site swelling*. These are labeled adverse events.

### *6.3 Data mining*

Data mining was performed to evaluate whether any reported events following the use of Hiberix were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the US VAERS Vac Name run with a data lock date of April 1, 2020 for Hiberix revealed one PT with a disproportional reporting alert, displayed in Table 6 (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

**Table 6: Data mining results**

| Preferred Term (PT) with EB05>2 | Number of Reports | Label* Status |
|---|---|---|
| Injection site discoloration | 19 | Unlabeled |

*Label dated May 8, 2019

All 19 reports (including 3 duplicate reports) were from a single reporter in Ohio and were non-serious events in pediatric patients. Reports were received in 2017. Most patients also received other concomitant vaccines. The healthcare professional reported injection site hyperpigmentation with appearance of “a black dot” after administration of Hiberix. Note that Hiberix is supplied in single-dose vials of lyophilized vaccine and accompanying saline diluent, but currently does not include syringes or needles. The reporter stated that after changing needles, this phenomenon did not occur anymore.

### *6.4 Periodic safety reports*

The manufacturer's postmarketing periodic safety reports for Hiberix were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

## 7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on April 28, 2020, for peer-reviewed literature, with the search term "Hiberix" and "safety" limited by human species, and dates from PAC trigger (January 14, 2016) to date of search (April 28, 2020), retrieved one publication pertaining to safety. No new safety concerns for Hiberix were identified in the review of these publications, summarized in the table below:

| Publication | Authors' Safety Conclusion |
|---|---|
| Klein NP, Abu-Elyazeed R, Cornish M, et al.<br><br>Lot-to-lot consistency, safety and immunogenicity of 3 lots of Haemophilus influenza type b conjugate vaccine: results from a phase III randomized, multicenter study in infants.<br><br>Vaccine. 2017 Jun 16; 35(28):3564-3574 | This phase III, randomized, multi-centered study evaluated the safety and immunogenicity of a monovalent tetanus toxoid-conjugate Hib vaccine (Hib-TT, Hiberix, GSK) compared to a monovalent (Hib-TT control, ActHIB, Sanofi Pasteur) and a combination Hib-TT vaccine containing diphtheria-tetanus-acellular pertussis (DTaP), inactivated poliovirus (IPV) and Hib-TT components (DTaP-IPV/Hib-TT; Pentacel, Sanofi Pasteur). The incidence and nature of reported adverse events were similar to data reported in the Vaccine Adverse Events Reporting Systems for monovalent Hib vaccine and were within normal range for common pediatric vaccine. The authors identified no safety signals following this study. |

## 8 CONCLUSION

This postmarketing pediatric safety review was triggered by the January 14, 2016 approval for the use Hiberix in children 6 weeks to 14 months of age. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Hiberix does not indicate any new safety concerns. Most adverse events are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

## 9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Hiberix.