U.S. FOOD & DRUG ADMINISTRATION

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

MEMORANDUM

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To:	Adamma Mba-Jonas, MD, MPH Chief, PVB, DE, OBE, CBER Deepa Arya, MD Acting Director, DE, OBE, CBER
Through:	Craig Zinderman, MD, MPH Associate Director for Product Safety, DE, OBE, CBER
Subject:	QUADRACEL Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC)
Sponsor:	Sanofi Pasteur, Inc.
Product:	QUADRACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine) Suspension for Intramuscular Injection
STN:	125525
Indication:	For active immunization against diphtheria, tetanus, pertussis and poliomyelitis. A single dose of QUADRACEL is approved for use in children 4 through 6 years of age as a fifth dose in the diphtheria, tetanus, pertussis vaccination (DTaP) series, and as a fourth or fifth dose in the inactivated poliovirus vaccination (IPV) series, in children who have received 4 doses of PENTACEL and/or DAPTACEL vaccine.

1. INTRODUCTION

1.1 Product Description

QUADRACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine) is a sterile suspension for intramuscular injection.

Each 0.5 mL dose is formulated to contain 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], and inactivated polioviruses [40 D-antigen units (DU) Type 1 (Mahoney), 8 DU Type 2 (MEF-1), 32 DU Type 3 (Saukett)]. QUADRACEL does not contain a preservative.

The four drug substances used to formulate QUADRACEL, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine (DTaP-IPV), are also included in US licensed PENTACEL® vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (DTaP-IPV-Hib).

1.2 Regulatory History

QUADRACEL was originally registered in Canada on March 20, 1997. This is the vaccine's international birthdate. The vaccine was subsequently approved in Australia, Canada, Hong Kong and New Zealand.

QUADRACEL was approved in the US on March 24, 2015, for use in children 4 through 6 years of age.

Under the US Pediatric Research Equity Act (PREA), the pediatric study requirement for children ages < 4 years and ≥ 7 to < 17 years of age was waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in these age groups and is not likely to be used in a substantial number of pediatric patients in these age groups.

No significant actions have been taken for safety reasons by the manufacturer or any regulatory authorities.

1.3 CDC Advisory Committee on Immunization Practices (ACIP)

ACIP recommends routine vaccination for tetanus, diphtheria, and pertussis. Infants and young children are recommended to receive a 5-dose series of diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines at 2, 4, 6, and 15-18 months, and 4-6 years. Persons aged 11-18 years should receive an adolescent booster dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/dtap.html

ACIP also recommends routine vaccination for poliovirus with an inactivated poliovirus vaccine (IPV). Infants and young children are recommended to receive a 4-dose series

administered at ages 2 months, 4 months, 6-18 months, and 4 through 6 years. Children should receive one dose of IPV between the ages of 4 through 6 years even if they have already received 4 doses of an IPV-containing combination vaccine product as an infant and toddler. www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/polio.html

2. OBJECTIVE

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the original 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 is the March 24, 2015, original approval in the US. This review will cover the time period of March 24, 2015, through December 31, 2017.

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

MATERIALS REVIEWED

Materials/documents evaluated for this review include:

- Vaccine Adverse Events Reporting System (VAERS) – reports of adverse events occurring after QUADRACEL vaccination received March 24, 2015 through December 31, 2017.

- Manufacturer's Submissions
  - QUADRACEL US package insert, dated March 2015
  - Letter regarding dose distribution data, dated May 14, 2018
  - Risk Management Plan, dated January 22, 2014
  - Periodic Benefit-Risk Evaluation Report, dated May 16, 2018

- FDA Documents
  - QUADRACEL Approval Letter, dated March 24, 2015
  - Review of QUADRACEL pharmacovigilance plan as part of original approval, dated November 26, 2014

- Publications (see Literature Search in section 8)

4. SAFETY-RELATED LABEL CHANGES IN REVIEW PERIOD

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

5. PRODUCT UTILIZATION DATA

The manufacturer estimates that from March 24, 2015, through December 31, 2017, approximately 1,350,230 doses of QUADRACEL were distributed worldwide. A total of 826,000 of these doses were distributed in the U.S. Of note, these data were provided by the manufacturer for FDA review, and doses distributed does not necessarily equal the total number of doses administered.

6. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

6.1 Sponsor's Pharmacovigilance Plan

Safety specifications from the sponsor's pharmacovigilance plan (PVP) include important identified risks of anaphylactic reaction, cellulitis, convulsion (including febrile convulsion), Henoch-Schönlein purpura and hypotonic-hyporesponsive episode (HHE). These events are being assessed via routine pharmacovigilance and reported in the Periodic Benefit Risk Evaluation Reports (PBRER). Anaphylactic reaction, cellulitis, convulsion (including febrile convulsion) and HHE are included in the label.

Guillain-Barre syndrome (GBS) and brachial neuritis are considered by the sponsor to be important potential risks based upon the 2011 US Institute of Medicine review of tetanus toxoid-containing vaccines which found "evidence inadequate to support or reject a causal relationship" between these events and the administration of tetanus toxoid-containing vaccines. Thus, GBS is included in the Warnings and Precautions section of the QUADRACEL label.

Additionally, the pharmacovigilance plan monitors for potential safety signals not identified in the clinical development studies or postmarketing experience, through routine monitoring of adverse event reports.

7. ADVERSE EVENT REVIEW

7.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of QUADRACEL between March 24, 2015, and December 31, 2017.

Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the number of doses administered, and lack of direct and unbiased comparison groups.

7.2 Results

The results of the VAERS search of adverse event reports for QUADRACEL during the review period are listed in Table 1 below.

Table 1: VAERS Reports for QUADRACEL (March 24, 2015 – December 31, 2017)

Age	Serious Non- Fatal*		Deaths		Non-serious		Total	
	US	Foreign	US	Foreign	US	Foreign	US	Foreign
0 to < 4 years	0	1	0	0	5	0	5	1
4 to < 7 years‡	2	5	0	0	100	0	102	5
7 to < 18 years	0	0	0	0	1	0	1	0
≥18 years	0	2	0	0	0	0	0	2
Unknown	1	0	0	0	5	0	6	0
Total	3	8	0	0	111	0	114	8

*Serious adverse events are defined in 21CFR600.80

‡QUADRACEL licensed indication age range is 4 through 6 years of age.

7.2.1 Deaths

No deaths have been reported.

7.2.2 Serious Non-fatal reports

During the reporting period, there were 11 serious non-fatal reports in QUADRACEL recipients; of the 10 reports where age at vaccination was reported, 8 (80%) occurred in patients <18 years old. Table 2 below lists the MedDRA (Medical Dictionary for Regulatory Activities, a standardized and clinically validated international medical terminology dictionary) adverse event terms, known by preferred terms (PTs), for the most frequent adverse events in these reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 2. Reported PTs (N ≥2) in Serious VAERS Reports for QUADRACEL (March 24, 2015 – December 31, 2017; <18 years of age)

MedDRA PT	Number of Reports	Label Status	Section of Label
Cold sweat	2	Unlabeled	---
Crying	2	Labeled	W&P[1]
Dysphagia	2	Unlabeled	---
Injection site erythema	2	Labeled	AR/CTE[2]
Lip swelling	2	Unlabeled	---
Local reaction	2	Unlabeled	---
Pallor	3	Labeled	AR/PME[3]
Pyrexia	2	Labeled	AR/CTE[2]
Rash	3	Labeled	AR/PME[2]
Urticaria	2	Labeled	AR/PME[2]

1. W/P: Warnings and Precautions
2. AR/CTE: Adverse Reactions, Clinical Trials Experience
3. AR/PME: Adverse Reactions, Postmarketing Experience (reported in the postmarketing period)

Each of the most frequent PTs in serious VAERS reports for QUADRACEL involved few reports. Many PTs were known, labeled events.

'Cold sweat' is not individually labeled; however, the two cases reporting this term include additional signs and symptoms consistent with vasovagal reactions. In children over 2 years of age, vasovagal reactions are clinically similar to hypotonic-hyporesponsive episode (HHE)[1], which has been observed after administration of pertussis-containing vaccines and is included in the warnings and post-marketing experience sections of the Quadracel label.

"Dysphagia" and "Lip swelling" are not individually labeled; however, hypersensitivity reaction is described in the label and each case reporting either of these terms includes additional signs and symptoms consistent with hypersensitivity reactions.

"Local reaction" is not individually labeled, however injection site reaction is described in the label, and each of the cases includes additional description of an injection site reaction.

Overall, no unusual frequency, clusters, or other trends for adverse events were identified from review of the serious reports. No new safety concerns were identified.

7.2.3 Non-serious reports

During the reporting period, there were 111 non-serious reports; of the 106 reports where age at vaccination was reported, 106 (100%) occurred in patients <18 years old. Table 3 below includes the 20 most frequently reported MedDRA preferred terms (PTs) for these reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

[1] DuVernoy TS, Braun MM and the VAERS Working Group. Hypotonic-Hyporesponsive Episodes Reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998. Pediatrics 2000 October;106(4):E52.

Table 3. Twenty most frequently reported PTs in non-serious VAERS reports for QUADRACEL (March 24, 2015 – December 31, 2017; <18 years of age)*

MedDRA PT	No. of Reports	Label
Injection Site Erythema	44	AR/CTE[2]
Injection Site Swelling	32	AR/CTE[2]
Injection Site Warmth	24	AR/CTE[2]
Injection Site Pain	19	AR/CTE[2]
Erythema	15	AR/CTE[2]
Pyrexia	15	AR/CTE[2]
Skin Warm	11	---
Rash	10	AR/PME[3]
Injection Site Reaction	9	AR/CTE[2]
Urticaria	9	AR/PME[3]
Injection Site Pruritus	8	AR/CTE[2]
Vomiting	8	---
Injection Site Rash	7	AR/CTE[2]
Swelling	7	AR/CTE[2]
Injection Site Induration	5	AR/CTE[2]
Headache	4	AR/CTE[2]
Injection Site Oedema	4	AR/CTE[2]
Pruritus	4	---
Fall	3	---
Febrile Convulsion	3	AR/PME[3]
Flushing	3	---
Induration	3	---
Injection site cellulitis	3	AR/PME[3]
Injection site urticaria	3	AR/PME[3]
Local Reaction	3	---
Pain	3	AR/CTE[2]
Pallor	3	AR/PME[3]
Peripheral Swelling	3	---
Wheezing	3	---

1. W/P: Warnings and Precautions
2. AR/CTE: Adverse Reactions, Clinical Trials Experience
3. AR/PME: Adverse Reactions, Postmarketing Experience (reported in the postmarketing period)

*Several terms tied in ranking so that more than 20 terms are listed.

The non-serious adverse events are consistent with those seen in the pre-licensure studies and are included in the package insert. Many of the most frequently reported non-serious events were related to vaccine administration, and consistent with injection site reactions (injection site erythema, injection site swelling, injection site warmth, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site induration, injection sites oedema, peripheral swelling, skin warm), and systemic reactions (pyrexia, pallor, headache). Both of these categories are labeled and include events which typically resolve quickly.

Several events are consistent with hypersensitivity reaction (pruritus, urticaria, vomiting, wheezing) as described in the Contraindications section and the Warnings and Precautions section.

Three cases described a fall at the clinic shortly after vaccination and the patients were noted to have pallor. Two of the cases describe syncope and one case describes transient lack of response to stimuli. All three cases are consistent with a vasovagal reaction following vaccination and/or HHE as reviewed in Section 7.2.2 of this review.

7.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of QUADRACEL 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 a data lock date of December 31, 2017, was conducted to identify PTs with disproportional reporting alerts for QUADRACEL (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

Data mining results: No disproportionality for QUADRACEL was observed in the Empirica database.

7.4 Periodic Benefit-Risk Evaluation Report (PBRER)

The manufacturer's postmarket periodic safety reports for QUADRACEL covering the surveillance period were reviewed. The adverse events reported in the periodic safety reports were consistent with those seen in VAERS. No additional safety issues were identified.

Since initial product licensure in 1997 through March 2018, the sponsor's world-wide postmarketing pharmacovigilance program has identified fourteen cases of anaphylactic reaction, thirty cases of cellulitis, fourteen cases of convulsion, three cases of Henoch-Schönlein purpura and six cases of HHE. No cases of GBS or brachial neuritis have been identified following administration of QUADRACEL.

8. LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on 04/10/2018 for peer-reviewed literature published between March 24, 2015, and December 31, 2017, with the search term "QUADRACEL" and no additional search parameters retrieved 2 articles. The titles and abstracts of these articles were reviewed. The two articles reported results of clinical trials which supported approval of the vaccine:

- Mosley JF, Smith LL, Parke CK, Brown JA, LaFrance JM, Clark PK. Quadracel: Vaccination Against Diphtheria, Tetanus, Pertussis, and Poliomyelitis in Children. Pharmacy and Therapeutics. 2016 Apr;41(4):238-53.

- Liang J, Wallace G, Mootrey G. Licensure of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine and Guidance for Use as a Booster Dose. Morbidity and Mortality Weekly Report. 2015 Sep 4;64(34):948-9.

9. CONCLUSION

This postmarketing pediatric safety review of QUADRACEL was triggered by the March 24, 2015, original approval. Most adverse event reports were non-serious and were consistent with the known safety profile of QUADRACEL. Review of passive surveillance adverse event reports, periodic safety reports, and the published literature for QUADRACEL does not reveal any new safety concerns.

10. RECOMMENDATIONS

FDA recommends continued routine safety monitoring of QUADRACEL.