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

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Epidemiology (OBE) Center for Biologics Evaluation and Research (CBER)
From:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	SmartPractice Denmark ApS
Product:	T.R.U.E. TEST (Thin-Layer Rapid Use Epicutaneous Patch Test)
STN:	103738/5208
Indication:	T.R.U.E. TEST® is an epicutaneous patch test indicated for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 6 years of age and older whose history suggests sensitivity to one or more of the 35 allergens and allergen mixes included on the T.R.U.E. TEST panels.
Meeting Date:	Pediatric Advisory Committee Meeting, September 2021

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 Thin-layer Rapid Use Epicutaneous Patch Test (T.R.U.E. TEST), BLA supplement 103738/5162 on August 25, 2017 for expansion of the indication to include use in persons 6 years of age and older.

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

Thin-layer Rapid Use Epicutaneous Patch Test (T.R.U.E. TEST) is a ready-to-use allergen patch test system consisting of 3 adhesive panels containing a total of 35 patches of allergens and allergen mixes and 1 negative control patch. Each test consists of three panels with 12 individual patches of allergen or allergen mixes or negative control, tape, foil pouch and desiccant. Panel 1.3 contains 11 allergens or allergen mixes and a negative control, Panel 2.3 contains 12 allergens or allergen mixes, and Panel 3.3 contains 12 allergens or allergen mixes.

T.R.U.E. TEST is indicated for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 6 years of age and older whose history suggests sensitivity to one or more of the 35 allergens and allergen mixes included on the T.R.U.E. TEST panels.

1.3 Regulatory History

- 1994: T.R.U.E. TEST was licensed in the U.S. for use in adults 18 years of age and older. It consisted of two panels containing 23 allergens and allergen mixes and one negative control. Since 1994, the number of allergens and allergen mixes contained in T.R.U.E. TEST has increased with approval of subsequent supplemental BLAs (sBLAs).
- 2007: sBLAs (STN 103738/5019 and 103738/5027) were approved to add a third panel (Panel 3.1), which included 5 new allergens and allergen mixes. The 2007 formulation contained a total of 28 allergens and a negative control.
    - Pediatric Study 1 was a postmarketing study to evaluate the safety and diagnostic performance of the 28 allergens and negative control contained in the 2007 formulation (STN 103738/5019) in at least 100 participants 6 to <18 years of age.

- 2012: sBLA 103738/5074 was approved to include 7 new allergens and allergen mixes; for a total of 35 allergens and allergen mixes and 1 negative control.
    - Pediatric Study 2 was a postmarketing requirement under Pediatric Research Equity Act (PREA) to evaluate the 7 new allergens in at least 110 participants 6 to <18 years of age.
- August 25, 2017: Approval of sBLA 103738/5162 to include use in persons 6 years of age and older. This approval is the trigger for 2021 PAC presentation.

2 MATERIALS REVIEWED

- FDA Adverse Event Reporting System (FAERS)
    - FAERS reports for T.R.U.E. TEST during August 25, 2017 to March 15, 2021 (PAC review period)
- Manufacturer's Submissions
    - T.R.U.E. TEST U.S. package insert; updated January 13, 2021
    - Applicant response to information request regarding dose distribution data, received April 26, 2021
    - Pharmacovigilance Plan, dated 2021
    - Periodic safety reports
- FDA Documents
    - STN 103738/5162 T.R.U.E. TEST Approval Letter, dated August 25, 2017
- Publications (see Literature Search in Section 7 below)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety-related labeling changes during August 25, 2017 to March 15, 2021 (PAC review period).

4 PRODUCT UTILIZATION DATA

SmartPractice Denmark provided distribution data[1] for the US during August 2017 – March 2021:

Patient population	Cartons sold	Estimated number of patients
Pediatric (< 18 years)	(b) (4)	
Adult (≥18 years)		

* SmartPractice Denmark estimated pediatric utilization data based on sales data to pediatric clinical sites: (b) (4) cartons were distributed to hospitals and clinics specializing in the pediatric population. Each multipack carton contains five units.. This method could underestimate pediatric use by not including pediatric usage of product sold to non-pediatric sites. It can also underestimate pediatric use since not all units may be utilized.

[1] These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

During the time period of August 2017 to December 2020, the total sales volume outside the U.S. was (b) (4) units. Of note, the product sold outside U.S. may be in different configurations, depending on the geographical region, and the allergen formulations contained on the panels and the adhesive tape may also differ from those on the U.S. product. Furthermore, T.R.U.E. TEST is not approved for pediatric patients outside of the U.S. and the sponsor has not received any reports indicating that this product is used off label in patients <18 years outside of the U.S.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP) is dated 2021.[2]
Important identified risks include:

- Sensitization to one or more of the allergens
- Acute allergic reactions, including anaphylaxis

The above risks are common to the product class, and both sensitization and acute allergic reactions are labeled under *Warnings and Precautions* and *Adverse Reactions* sections of the package insert.

There are no important potential risks for this product. Missing information includes use of T.R.U.E. TEST during pregnancy or in nursing mothers.

The safety risks for T.R.U.E. TEST are 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 postmarketing requirement (PMR) safety-related studies under Food and Drug Administration Amendments Act (FDAAA) of 2007 or Risk Evaluation and Mitigation Strategy (REMS) for this product. There are no outstanding postmarketing commitment (PMC) safety-related studies for T.R.U.E. TEST.

5.2 Postmarketing Studies

The sponsor has fulfilled the pediatric study requirement for all relevant pediatric age groups.

- A partial waiver was granted for the pediatric study requirements under Pediatric Research Equity Act (PREA) for ages birth to < 6 years of age, because necessary studies are impossible or highly impracticable because the number of children younger than 6 years of age with allergic contact dermatitis is small.
- Approval of sBLA 103738/5162 to include use in persons 6 years of age and older (the regulatory trigger for this PAC review) was based on two postmarketing pediatric studies:
    - Pediatric Study 1 was conducted to evaluate the safety and diagnostic performance of the 28 allergens and negative control contained in the

[2] Submitted in response to information request dated April 5, 2021, under STN 103738/5208.

2007 formulation (approved under STN 103738/5019) in at least 100 participants 6 to <18 years of age.

- Pediatric Study 2 was conducted to evaluate the safety and diagnostic performance of the 7 new allergens included in the 2012 formulation (approved under 103738/5074) in at least 110 participants 6 to <18 years of age.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for AE reports following the use of T.R.U.E. TEST between August 25, 2017 (PAC trigger) to March 15, 2021. FAERS stores postmarketing AE and medication error reports submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every AE or medication error that occurs with a product. 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 product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of AE reports for T.R.U.E. TEST during the PAC review period are listed in Table 1 below. There were a total of 9 non-serious US reports for review period August 25, 2017 to March 15, 2021. None of the reports involved pediatric patients.

Table 1: FAERS Reports for T.R.U.E. TEST during August 25, 2017 to March 15, 2021

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18 years	0	0	0	0	0	0	0	0
≥18 years	0	0	0	0	6	0	6	0
Unknown	0	0	0	0	3	0	3	0
All ages	0	0	0	0	9	0	9	0

*Note: Serious non-fatal adverse events include otherwise medically important conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.

6.2.1 Non-serious Reports

During the reporting period, there were 9 non-serious reports; 6 of which involved adult patients and age was unknown for the remaining 3 reports. The 9 reports were associated with a total of 13 Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) and Table 2 below displays the PTs occurring in > 1 report. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 2: Most frequently reported PTs in non-serious reports

Preferred Term (PT)	Number of Reports	Label* Status
Administration Site Reaction	3	Unlabeled**
Erythema	2	Labeled (Adverse Reactions)
False Positive Investigation Result	2	Not applicable (PT does not represent an adverse event)

*Label updated January 13, 2021

**The PT for *Administration site reaction* is related to labeled events under Warnings and Precautions: Acute Allergic Reactions (include localized reactions); Sensitization, Extreme Positive Reactions, Excited Skin Syndrome, Tape Reactions, Irritant Contact Dermatitis.

There were no new safety concerns from review of PTs for non-serious reports.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of T.R.U.E. TEST were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure (1994) through the data lock point as of April 25, 2021. (Data mining query was performed on May 2, 2021 with data as of April 25, 2021). Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Product Name (S) run identified 9 preferred terms (PTs) summarized in Table 4, with a disproportional reporting alert. (Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean). Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Data mining results

Preferred Term (PT) with EB05 > 2	Number of Reports	Label* Status
Application site reaction	75	Unlabeled
Skin disorder	14	Unlabeled
Dermatitis contact	7	Labeled (1 Indications and Usage)
Hypersensitivity	24	Labeled (12.1 Mechanism of Action)
Administration site reaction	3	Unlabeled
Dermatitis	44	Unlabeled
Pruritus	31	Labeled (*Itching* is labeled in 6 Adverse Reactions)
Dermatitis bullous	8	Unlabeled
Urticaria	16	Labeled (Warnings and Precautions; under 5.1 Acute Allergic Reactions)

*Label updated January 13, 2021

The PTs for *Application site reaction*, *Administration site reaction*, and *Skin disorder* may be related to labeled events under Warnings and Precautions: Acute Allergic Reactions (including localized reactions), Sensitization, Extreme Positive Reactions, Excited Skin Syndrome, Tape Reactions, Irritant Contact Dermatitis. The PT for *Dermatitis contact* is confounded by the labeled indication for diagnosis of allergic contact dermatitis. The PT for *Dermatitis* is related to the indication for *Acute contact dermatitis,* and could also be a symptom of the labeled events *Irritant contact dermatitis* (Warnings and Precautions) or *Ectopic flare of pre-existing dermatitis* (Adverse Reactions). The PT for *Dermatitis bullous* is related to the labeled event Excited Skin Syndrome (which describes bullous reactions).
There were no new safety concerns from review of the data mining results.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for T.R.U.E. TEST were reviewed. Additional adverse events reported in periodic adverse experience reports (PAERs) are described below.

PAER for reporting interval	Attached MedWatch forms [Associated PT(s)*]
December 1, 2016 to November 30, 2017	None
December 1, 2017 to November 30, 2018	1 non-serious report [Vertigo]
December 1, 2018 to November 30, 2019	2 non-serious reports [Administration site reaction]
December 1, 2019 to November 30, 2020	None

None of the reported AEs involved pediatric patients. The AEs reported were consistent with those seen in FAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons during the PAC review period.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on May 2, 2021, for peer-reviewed literature, with the search term "T.R.U.E. TEST" or "Thin-layer Rapid Use Epicutaneous Patch Test" and "safety" limited by human species, and dates from August 25, 2017 (PAC trigger) to date of search May 2, 2021, did not identify any publications pertaining to safety for the T.R.U.E. TEST product.

8 CONCLUSIONS

This postmarketing pediatric safety review was triggered by the August 25, 2017 approval of sBLA 103738/5162 for expansion of the indication to include use in persons 6 years of age and older. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for T.R.U.E. TEST does not indicate any new safety concerns. There were no reports of AEs in children. There were no reports of serious AEs. Few non-serious AEs were reported. 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 T.R.U.E. TEST.