Summary Basis for Regulatory Action

Date: March 2, 2017

From: CDR Elizabeth J. Valenti, MPH, RAC (U.S.), Chair of the Review Committee

BLA/ STN#: 125579/0

Applicant Name: SmartPractice Denmark ApS

Date of Submission: January 5, 2006

Proprietary Name/ Established Name: Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test

Indication: For use as an aid in the diagnosis of allergic contact dermatitis in persons 6 years of age and older whose history suggests sensitivity to one or more of the five substances included on the Rubber Panel T.R.U.E. TEST.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Marion F. Gruber, PhD, Director, Office of Vaccines Research and Review

X I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted Reviewer Name – Document Date	**Specific documentation used in developing the SBRA**
Clinical Review	Bo Chi, MD 6/9/06 Joohee Lee, MD 5/17/16
Clinical Statistical Review	Ghideon Solomon, PhD 2/16/16
CMC Review	Jay Slater, MD 10/19/06 Taruna Khurana, PhD 2/22/16 Alfred Del Grosso, PhD 3/15/16 & 3/31/16
Bioresearch Monitoring Review	Colonious King 2/18/16
Facilities and CMC Review	Richard Heath Coats 12/19/14 & 5/11/16 & 2/22/17
Pharmacovigilance Review	Patricia Rohan, MD 12/8/15

Advertising and Promotional Labeling Review	Kristine Khuc, PharmD 11/26/16 Oluchi Elekwachi 1/7/16
Proprietary Name Review	Oluchi Elekwachi 2/20/16
Approved Draft Labeling	Christina Houck 2/13/17

1. Introduction

Rubber Panel T.R.U.E. TEST® (Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test) is an epicutaneous patch test. The proposed indication is for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons six years of age and older whose history suggests sensitivity to one or more of the five substances included on the Rubber Panel T.R.U.E. TEST. The proper name is Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test and the proposed proprietary name is Rubber Panel T.R.U.E. TEST.

The Rubber Panel T.R.U.E. TEST test kit contains one multi-patch panel that contains five rubber allergen patches and a negative control. Each panel contains one negative control and five rubber allergens: Carba mix, 0.25 mg/cm^2; Black Rubber mix, 0.075 mg/cm^2; Mercaptobenzothiazole, 0.075 mg/cm^2; Mercapto mix, 0.075 mg/cm^2; and Thiuram mix, 0.027 mg/cm^2. Each allergen substance is mixed in a vehicle, either hydroxypropyl cellulose or polyvidone, to make a gel. Currently approved and marketed by the applicant is a similar product, T.R.U.E. TEST (Thin-Layer Rapid Use Epicutaneous Patch Test). The currently approved configuration of T.R.U.E. TEST consists of 35 allergens on three panels (1.3, 2.3, and 3.3). It is indicated as a patch test to use as an aid in the diagnosis of ACD in persons 18 years of age and older whose history suggests sensitivity to one or more of the 35 substances included on the T.R.U.E. TEST panels. T.R.U.E. TEST Panel 1.3 contains 11 allergen patches and a negative control. T.R.U.E. TEST Panels 2.3 and 3.3 each contain 12 allergens patches.

The five rubber allergens included on the Rubber Panel T.R.U.E. TEST are also included on the original T.R.U.E. TEST product, Panels 2.3 and 3.3. Data from adult subjects for T.R.U.E. TEST was used to support the indication in adults for Rubber Panel T.R.U.E. TEST. For the pediatric clinical study, noted below, conducted to support the pediatric indication of the Rubber Panel T.R.U.E. TEST, the applicant used panels 1.1, 2.1, and 3.1, which contained 28 allergens and a negative control, and was the licensed configuration at the time of the study. The five rubber allergens included in Rubber Panel T.R.U.E. TEST were contained on Panel 2.1 at the time of the adult and pediatric studies. The panels have since been approved to be labeled Panels 1.3, 2.3, and 3.3.

Prominent issues that arose during the review of this file included sufficient stability data to support expiration dating, documentation regarding combination product regulations, and the acceptability of the clinical, statistical, and manufacturing data used to support the inclusion of these five rubber allergens from T.R.U.E. TEST for the approval of Rubber Panel T.R.U.E. TEST. These issues were resolved during the review. In addition, pediatric data were reviewed in order to support a pediatric indication and a partial waiver was granted, which resolved the need for further pediatric studies. Labeling was reviewed and revised. The labeling includes a contraindication for patients with a history of severe allergic reaction

(systemic and/or local) to any of the allergen components or inactive substances in Rubber Panel T.R.U.E. TEST.

2. Background

Allergic contact dermatitis (ACD) is a common inflammatory skin condition with a non-specific presentation of pruritic eczema with variable distribution throughout the body. ACD is driven by a delayed type (IV) hypersensitivity reaction, and T lymphocytes are central to the current model of ACD pathogenesis. ACD reactions normally appear 9 to 96 hours after exposure. Current epidemiological estimates suggest that ACD occurs in adults and adolescents at similar rates of 20% and 15% respectively. A number of studies suggest that ACD is more common in children 6 years of age and older than previously assumed.

Diagnosis of ACD begins with clinical suspicion based on history and physical exam. Although the history and physical exam are important, clinical evaluation does not reliably differentiate irritant contact dermatitis (ICD) from ACD. Patch testing is used as an aid to the diagnosis of ACD. ACD is distinct from latex hypersensitivity, which is mediated by IgE. By contrast, ACD is mediated by T-cells, and IgE is not involved.

Rubber-containing products contain a range of chemicals intended to convert natural rubber into more durable polymers. The contact allergens included in the Rubber Panel T.R.U.E. TEST are the residues of chemicals used in manufacturing a rubber product. The five Rubber Panel T.R.U.E. Test allergens are ubiquitous chemicals used in rubber manufacturing that can act as T cell antigens. In adults, ACD due to rubber is commonly due to occupational exposure and typically affects the hands. For children, rubber allergens are among the specific relevant allergens to consider when the distribution of the dermatitis includes the lower legs and feet.

The Rubber Panel T.R.U.E. TEST is covered with a protective sheet and packaged in an aluminum foil pouch with a desiccant for moisture control. In addition to the package insert, an identification template is included with the product, and used as a physical guide for verifying allergen identity by position and scoring reactions after panel removal. Rubber Panel T.R.U.E. TEST is applied to a patient's back or upper arm. After 48 hours, the patch is removed and skin reactions are recorded. Reactions are recorded again at 72-96 hours after application.

Regulatory History

Mekos Laboratories AS (Mekos) submitted a supplement to their BLA for the original Thin-Layer Rapid Use Epicutaneous Patch Test (T.R.U.E. TEST®) (STN 103738/5031) on January 5, 2006 and it was received on January 9, 2006.

Due to CMC issues, a Complete Response (CR) Letter was issued on June 30, 2006 and Mekos responded on August 14, 2006. Continued CMC issues and the lack of a plan to address the Pediatric Research and Equity Act (PREA) requirements resulted in a second CR Letter, issued on February 12, 2007. The applicant changed the company name from Mekos Laboratories AS to SmartPractice Denmark ApS (SmartPractice)

during the review process. This change was accepted on February 28, 2013, STN 103738/5098. On June 7, 2013 SmartPractice was advised that upon receipt of the response to the February 2007 CR Letter, the supplement would be converted to a new BLA; however, the CR review clock (6 months) would still apply. CBER agreed to accept descriptive efficacy and safety data in adults from the approval of the original T.R.U.E. TEST to support the adult indication for Rubber Panel T.R.U.E. TEST. SmartPractice responded to the second CR Letter on August 19, 2014. The original PAS, STN 103738/5031, was converted to a BLA, STN 125579/0, in November 2014 and communicated to the applicant on December 2, 2014. A third CR Letter was issued on January 12, 2015 due to outstanding clinical, CMC, and facilities issues. SmartPractice responded to the third CR Letter on August 25, 2015. A new review goal date of February 26, 2016 was established. However, on February 26, 2016 SmartPractice was informed that CBER would not meet the goal date, but would continue the review of the file in an expeditious manner to review and address all outstanding issues. This is a non-PDUFA product; therefore, PDUFA mandated review time frames to not apply.

Given that the original supplement was converted to a new BLA, the clinical data in support of this Rubber Panel T.R.U.E. Test BLA is based on the clinical data previously approved for the five applicable rubber panel allergens that are included on the currently licensed T.R.U.E. TEST product, indicated for adult patients. The T.R.U.E. TEST is currently approved for use as an aid in the diagnosis of ACD in persons 18 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. T.R.U.E. TEST is not indicated for patients less than 18 years of age.

The applicant conducted a Phase 3 pediatric study with the T.R.U.E. TEST product that was approved at the time of study commencement in 2007. This study included pediatric subjects 6 through 17 years of age. T.R.U.E. TEST Panels 1.1, 2.1, and 3.1 were applied to subjects' backs. The patch consisted of three panels that contained 28 allergens and a negative control, which was the approved product at that time. T.R.U.E. TEST is not approved for use in pediatric patients. However, the five rubber allergens were studied; therefore, data is available for the complete Rubber Panel T.R.U.E. TEST and a pediatric indication was sought in patients 6 years of age and older.

In addition, the applicant was required to address certain Quality System Regulations (QSR's) for devices such as the T.R.U.E. TEST product is classified as a combination product.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The basic manufacturing process for the allergen patches included on the Rubber Panel T.R.U.E. TEST is unchanged from that of the T.R.U.E. TEST. All five rubber patches are currently on the approved T.R.U.E Test Panels 2.3 and 3.3. There is no change in the formulations of these rubber allergen patches and the applicant states that no changes will be made to the already approved T.R.U.E. TEST.

The allergen components and concentrations are provided in Table 1 below.

Table 1: Description of Rubber Panel Allergen Patches

Rubber Panel Allergens	**Labeled Concentration**	**Allergen Components**	**Vehicle**
Carba Mix	0.25 mg/cm^2	Diphenylguanidine (DPG) Zincdibutyldithiocarbamate (ZDB) Zincdiethyldithiocarbamate (ZDE)	Hydroxypropyl cellulose
Black Rubber Mix	0.075 mg/cm^2	N-isopropyl-N'-phenyl paraphenylenediamine Cyclohexyl-N'-phenyl paraphenylenediamine Diphenyl paraphenylene-diamine	Polyvidone
Mercapto-benzothiazole	0.075 mg/cm^2	Mercaptobenzothiazole	Polyvidone
Mercaptomix	0.075 mg/cm^2	N-cyclohexylbenzothiazyl-sulfenamide Dibenzothiazyl disulfide Morpholinylmercaptobenzothiazole	Polyvidone
Thiuram Mix	0.027 mg/cm^2	Tetramethylythiuram monosulfide Tetramethylthiuram disulfide Disulfiram Dipentamethylenethiuram disulfide	Polyvidone

Information regarding source material specifications, drug substance, (b) (4) assays, and product stability was included in the January 2006 original submission. One of the primary deficiencies identified (June 30, 2006 and February 12, 2007 CR Letters) was that the expiration dating of the rubber panel needed to be based on real time stability data of the final assembled product. CBER did not concur with the applicant's proposal to submit stability data from their currently licensed T.R.U.E. TEST panel 2.3. Rather, stability data in the proposed new rubber panel configuration was required. In order to establish expiry dating in support of approval, CBER required real-time stability data on the Rubber Panel T.R.U.E. TEST. The data was submitted and found to be acceptable.

Manufacture of Drug Substance

The Drug Substance (DS) manufacturing process used for the Rubber Panel T.R.U.E. TEST allergens (Carba mix, Black Rubber mix, Mercaptobenzothiazole, Mercapto mix, and Thiuram mix) is the same as used in the manufacture of the currently licensed T.R.U.E. TEST panels. The DS manufacturing and process validations were conducted in 1999 and 2001 for the T.R.U.E. TEST products.

Analytical reports and certificate of analysis (CoA) for each of the source material were provided.

The DS is defined as (b) (4)

The allergen gel manufacturing process was validated for the following critical process steps:

- (b) (4)
- (b) (4)

Allergen gel (b) (4) . The results were within validation acceptance criteria as indicated in Table 2 below.

Table 2: Process validation acceptance criteria

(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)

The allergen gel manufacturing process was also validated for T.R.U.E. TEST panels. The process validation demonstrated (b) (4) and all the batches met the acceptance criteria of relative standard deviation (RSD) (b) (4).

The drying procedure of the gel (b) (4) was validated for the T.R.U.E. TEST panels. The results for (b) (4) remain within acceptance criteria under all tested drying conditions. No deviations were noted for the tested allergens of the Rubber Panel.

Manufacture of Drug Product

The Drug Product (DP) manufacturing process used for the Rubber Panel T.R.U.E. TEST allergens (Carba mix, Black Rubber mix, Mercaptobenzothiazole, Mercapto mix, and Thiuram mix) is the same as used in the manufacture of the currently licensed T.R.U.E. TEST panels.

The allergen gel (b) (4) (DS) are (b) (4) out into allergen gel patches (0.9 cm x 0.9 cm) (0.81 cm^2). The patches are placed onto predefined locations on the surgical tape, specified for each allergen. The tape is marked with a panel orientation arrow, covered with protective foil, and cut into test panels. The panels are packed into labeled laminated foil pouches that are (b) (4) for sealing. The sealed foil pouch is placed in a plastic wrap with a reading guide, and then sealed. This sealed plastic

wrap is packed into labeled cartons. Rubber Panel T.R.U.E. TEST is marketed in a multipack carton containing five units. Each unit consists of one adhesive panel containing six patches. The final batch size is (b) (4) units. Each patch is tested by a specific analytical method with acceptance criteria of (b) (4) of its labeled value at the release, specified in Table 3 below.

Table 3: Release specifications of Rubber Panel Allergen Patches

Allergen	**Tests**	**Release limits (mg/cm^2)**
Carba Mix	Transparent colorless or almost colorless	(b) (4)
Black Rubber Mix	Transparent yellowish brown	(b) (4)
Mercaptobenzothiazole	Transparent colorless or almost colorless	(b) (4)
Mercapto Mix	Transparent colorless or almost colorless	(b) (4)
Thiuram	Transparent colorless or almost colorless	(b) (4)
Negative Patch	Transparent colorless	Not detected
Content Uniformity for (b) (4)	(b) (4)	(b) (4)
Content Uniformity for (b) (4)	(b) (4)	(b) (4)
Microbial Test	(b) (4) microorganisms/test Absence of (b) (4) Absence of (b) (4)	 Yes Yes

The major CMC review issues included in the June 30, 2006 and February 12, 2007 CR Letters were with regard to the need for sufficient stability data for the final product. The applicant submitted sufficient data and lots for testing. Final DP shelf

life is 24 months from the date of manufacture for storage at room temperature, 68 – 77 °F (20 – 25°C).

Additional CMC review issues that were included in the January 12, 2015 CR Letter and were resolved during the review of this BLA, included an update to the concentration of thiuram mix based on an approved change to T.R.U.E. TEST; the review of batch records, manufacturing process flow, and the chemical assays and tests used for stability studies; and the request and submission of complete analytical methods and validations for the five rubber allergens to this BLA for completeness, although they are identical to those under the T.R.U.E. TEST BLA.

Combination Product
The Rubber Panel T.R.U.E. TEST is categorized as a combination product under 21 CFR 3.2(e); therefore, the product is subject to both the Current Good Manufacturing Practice (cGMP) regulations (21 CFR 211) and the device Quality System Regulation (QSR) (21 CFR 820). The applicant performed a gap analysis of the current Quality System, including Management responsibilities (§820.20), Design controls (§820.30), Purchasing controls (§820.50), and Corrective and preventive action (§820.100). The cGMP regulations and QSRs requirements demonstrated by the applicant are acceptable for licensure of this product.

b) CBER Lot Release
The lot release protocol template for the final packaged Rubber Panel T.R.U.E. TEST product was submitted to CBER for review and found acceptable after revisions. Samples were submitted to CBER in support of the BLA, tested by CBER and found to be acceptable.

For routine lot release, the applicant will submit samples together with lot release protocols. A lot testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection
Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Rubber Panel T.R.U.E. Test are listed in the table below. The activities performed and inspectional history are noted in the table and are further described in the paragraph that follows.

Table 4: Manufacturing Facilities for Rubber Panel T.R.U.E. Test

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Drug Product and Drug Substance Manufacturing *Drug Product*	3003216248	N/A	Waived	Team Biologics January 25-29, 2016

Labeling and Testing SmartPractice Denmark ApS Herredsvejen 2 3400 Hillerod Denmark				

Team Biologics conducted a surveillance inspection of SmartPractice Denmark ApS from January 25-29, 2016. The inspection was classified as VAI. All inspectional issues were resolved.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(b). The FDA concluded that this request is justified as the manufacturing of this product will meet the quantitative criteria for the Expected Environmental Concentration and no extraordinary circumstances exist that would require an environmental assessment.

e) Container Closure System

The Rubber Panel T.R.U.E. Test panel is covered by a protective sheet and sealed in a pouch of laminated foil. A desiccant paper is included in the package for stability. Stability studies support a room temperature shelf life of 24 months.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted as part of this supplement.

5. Clinical Pharmacology

No new clinical pharmacology data were submitted as part of this supplement.

6. Clinical/ Statistical

The Rubber Panel T.R.U.E. TEST consists of one adhesive panel that contains five allergens on individual patches. These five rubber allergens are included in the original T.R.U.E. TEST panels, licensed in adults in 1994 under STN 103738 and CBER agreed to accept that data for adults. In order to fulfill requirements under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the applicant conducted a study in children 6 through 17 years of age and requested a partial waiver for children less than six years of age.

To support licensure of the Rubber Panel T.R.U.E. TEST in pediatric subjects 6 years of age and older, the applicant submitted data from an open-label, single-site Phase 3 trial of T.R.U.E. TEST panels 1.1, 2.1, and 3.1 (Mekos 07 29P1/2/3 401) in 102 pediatric subjects (6 through 17 years of age) with suspected ACD and previous histories of ACD, ICD, and atopic dermatitis.

a) Clinical Program

The descriptive efficacy data to support licensure of the five rubber allergens on Rubber Panel T.R.U.E. TEST in adults 18 years of age and older were collected under five clinical studies conducted under U.S. Investigational New Drug (IND) applications in North America and Europe, and submitted to and reviewed under STN 103738 and approved for use in the U.S. in 1997. In order to clarify and reevaluate data from only these five rubber allergens in adults, multiple information requests (IRs) were sent to the applicant. This issue was resolved and resulted in the descriptive efficacy data in adults properly reported in the package insert (PI).

In these studies, 466 adults with ACD were patch tested to at least 1 of the 5 rubber allergens. Efficacy data for the rubber allergens come from consecutive subjects with a history and exam consistent with ACD, without selecting for individuals with known rubber allergen exposure. Positive reaction rates for the five rubber allergens ranged from 1.7% (Black Rubber mix) to 4.1% (Thiuram mix).

b) Pediatrics

Under PREA, this application is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups unless the requirement is waived, deferred, or inapplicable. In the February 12, 2007 CR Letter, the applicant was advised of this PREA requirement. The applicant conducted a study in pediatric subjects under U.S. IND application 13546, originally submitted to CBER on November 6, 2007. The applicant subsequently evaluated the safety and efficacy of the original T.R.U.E. TEST in a Phase 3 study under this IND, with the intention to support U.S. licensure. On June 11, 2012 the applicant was advised that the May 10, 2012 submission was considered an incomplete response, in part because it lacked pediatric data. CBER noted that the applicant's first pediatric study was complete and the study design included the five allergens on the Rubber Panel T.R.U.E. TEST. CBER requested that the applicant submit the pediatric data and seek a pediatric indication.

To support licensure of this BLA in pediatric subjects and in response to the February 12, 2007 CR Letter, the applicant submitted data from an open-label, single-site Phase 3 trial of T.R.U.E. TEST panels 1.1, 2.1, and 3.1 (28 allergens) (Mekos 07 29P1/2/3 401) in 102 pediatric subjects (6 through 17 years of age) with suspected ACD and previous histories of ACD (97.1%), ICD (25.5%), and atopic dermatitis (53.9%). Panel 1.1 contained the negative control and Panel 2.1 contained the five patches of rubber allergens included on the Rubber Panel T.R.U.E. TEST.

The primary objective of the study was to characterize the diagnostic performance and safety of 28 substances, including the 5 rubber-related substances, in T.R.U.E. TEST Panels 1.1, 2.1, and 3.1.

The mean and median age of the 102 subjects enrolled in the trial was 11.6 years and 11 years, respectively. Age representation was evenly distributed across the eligible age range; 45 (44.1%) subjects were 13 to 17 years old, 29 (28.4%) were 9 to 12 years old, and 28 (27.5%) were 6 to 8 years old. Females comprised 52% of the trial population. Forty subjects were identified as Caucasian (39.2%) and 32 subjects as Hispanic (31.4%). The remaining 40 subjects were identified as Asian (n=13; 12.7%), Other (n=10; 9.8%), and African-American (n=7; 6.9%).

All enrolled subjects had placement of three licensed T.R.U.E. TEST panels 1.1, 2.1, and 3.1 on the back or upper arm on Day 0 (Visit 1). Subjects returned on Day 2 for panel evaluation and removal (Visit 2). Of the 102 subjects, 101 subjects presented two days later for patch removal and assessment of panel adhesion and tolerability. Test site reactions were evaluated at three time points after patch application: 3 to 4 days, 7 days, and 21 days. Skin reactions were evaluated using standard patch test interpretation guidelines established by the International Contact Dermatitis Research Group (ICDRG) and scored as negative, irritant, doubtful, or positive (+, ++, +++ based on intensity) by the investigators 3-4 and 7 days after patch application.

Positive reaction frequencies among the 101 subjects were as follows: 7% to Carba mix; 6% to Thiuram mix; and 2% each to Black Rubber mix, Mercaptobenzothiazole, and Mercapto mix. One subject had a positive reaction to Thiuram mix seven days after patch application. No subjects had a reaction on Day 21. Seventeen consecutive subjects who completed the protocol had positive reactions to at least one of the five rubber allergens. This frequency is similar to that reported in adults.

The study design did not include pre-specified criteria for efficacy because the population did not consist of individuals with known ACD due to rubber allergen(s); however, the descriptive efficacy and safety data demonstrate that Rubber Panel T.R.U.E. TEST can aid in the diagnosis of ACD.

Multiple IRs sent to the applicant requested clarification in regard to the conduct and scoring of the pediatric study. The applicant's responses resulted in reporting the appropriate information for children six through 17 years of age in the PI.

In addition to submission of the study above, the applicant requested a partial waiver for children less than six years of age because studies in this age group would be impossible or highly impracticable. On February 3, 2016 the applicant's pediatric plan was presented to the Pediatric Review Committee (PeRC), who agreed with CBER's decision to grant the partial waiver in children less than six years of age.

Bioresearch Monitoring
During the review of the BLA, the single domestic clinical study site was inspected under the Agency's Bioresearch Monitoring program. No discrepancies were observed between the source documents and data submitted. The inspection did not reveal significant problems that impacted the data submitted in this BLA.

7. Safety

a) Adults
The safety data to support licensure of the Rubber Panel T.R.U.E. TEST in adults 18 years of age and older were collected under five clinical studies conducted in North America and Europe under U.S. INDs, and submitted to and reviewed under STN 103738. In order to clarify and reevaluate data from only the five Rubber Panel T.R.U.E. TEST allergens in adults, multiple information requests (IRs) were sent to the applicant. The issues were resolved and resulted in safety data in adults being properly reported in the package insert (PI). The most common adverse reactions (occurring in more than 1% of the adult study population) were erythema, pruritus, hyperpigmentation, and tape irritation.

b) Pediatrics
In the pediatric study, subjects were followed for 21 days after enrollment. Following patch placement on Day 0 (Visit 1), subjects returned on Day 2 for panel evaluation and removal (Visit 2). Panel adhesion was evaluated and characterized using a five-point scale based on degree of skin-to-panel contact and tape edge adherence. Panel adhesion was graded as excellent (complete adhesion), good, fair, and poor (the panel fell off). Evaluation and grading of test site skin reactions were performed at Day 3 (Visit 3), Day 7 (Visit 4), and Day 21 (Visit 5). If necessary to verify site reactions at Day 3, subjects returned the following day for an additional evaluation (Visit 3b). Safety endpoints were monitored for up to 19 days, starting at Visit 2 and ending at Visit 5.

With respect to safety, the majority of subjects (91 to 96%) had excellent to good adhesion to Panels 1.1, 2.1, and 3.1. The majority of subjects (81 to 82%) had none or weak tape irritation at the panel application sites. The rubber allergen patches on Panel 2.1 were well tolerated. All adverse events related to the rubber allergens (n=8; 8%) were mild to moderate in severity. Dermatitis flares were the most commonly reported adverse event in pediatric subjects. Seven of the 44 dermatitis flares reported occurred in the setting of a positive reaction to Carba mix (n=5, Black Rubber mix (n=1), and Thiuram mix (n=1). Attribution of flares to specific allergens to which subjects tested positive could not be reliably assessed.

No persistent or late reactions to any of the Rubber Panel T.R.U.E. TEST allergens were observed within 21 days. No subject was discontinued from the study due to an AE. No serious adverse events (SAE) or deaths occurred. Two subjects dropped out of the study. One subject withdrew consent and the other was lost to follow-up.

Multiple IRs requested clarification in regard to events reported for the pediatric study and reevaluation of adult data. The applicant's responses resulted in reporting the appropriate safety information for adults and children 6 through 17 years of age in the PI. The PI contains a contraindication for patients with a history of severe allergic reaction (systemic and/or local) to any of the allergen components or inactive substances of Rubber Panel T.R.U.E. TEST.

8. Advisory Committee Meeting

There were no issues pertaining to this supplement that required input from the Allergenic Products Advisory Committee.

9. Other Relevant Regulatory Issues

None.

10. Labeling

a) Proprietary Name

The proposed proprietary name for the product, Rubber Panel T.R.U.E. TEST, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on February 25, 2016, and found to be acceptable. OVRR communicated the acceptability of the proprietary name to the applicant on February 26, 2016.

b) Conclusions of APLB and Committee Review of Draft Package Insert and Other Labeling

The APLB found the PI and carton/container labels to be acceptable from a promotional and comprehension perspective. The review committee required revisions to the PI, included limiting adult and pediatric data to the five rubber allergens. All issues were acceptably resolved after exchange of information and discussions with the applicant. No issues were identified with the proposed carton and container labeling.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The Review Committee recommends that Rubber Panel T.R.U.E. TEST be approved for licensure.

b) Risk/ Benefit Assessment

No safety signals for serious adverse events were identified and the safety profile of the Rubber Panel T.R.U.E. TEST allergens in children is comparable to that of adults who have used the original T.R.U.E. TEST product. The observed adverse reactions following patch testing were mild and self-limited, and are described in the package insert. The Rubber T.R.U.E. TEST induces positive reactions within 3 days to rubber

allergens in persons with suspected ACD. Rubber Panel T.R.U.E. TEST presents a favorable overall risk-benefit profile and offers the first patch test for use in persons younger than 18 years of age.

c) Recommendation for Postmarketing Risk Management Activities

There is no recommendation for postmarketing risk management activities.

d) Recommendation for Postmarketing Activities

There is no recommendation for postmarketing activities.