*****Double-click here if you do not see the Add-Ins tab on the toolbar ribbon*****

Application Type	BLA
STN	125579
CBER Received Date	January 9, 2006
Goal Date	Non-PDUFA
Division / Office	DVRPA/ OVRR
Priority Review	No
Reviewer Name(s)	Joohee Lee MD
Review Completion Date / Stamped Date	May 17, 2016
Supervisory Concurrence	Roshan Ramanathan MD, MPH
	Jeff Roberts, MD
Applicant	SmartPractice Denmark ApS
Established Name	Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test
(Proposed) Trade Name	Rubber Panel T.R.U.E. TEST
Pharmacologic Class	Contact Dermatitis Patch Test
Formulation(s), including Adjuvants, etc	Patch
Dosage Form(s) and Route(s) of Administration	One adhesive panel consisting of 5 allergen and allergen mix patches and a negative control.
Dosing Regimen	Apply the adhesive panel of allergens on healthy skin of the back. Remove panels and evaluate the skin 48 hours after application. Re-evaluate the skin 72 to 96 hours after application
Proposed Indication(s) and Intended Population(s)	Rubber Panel 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 5 substances included on the Rubber Panel T.R.U.E. Test.
Orphan Designated	No

TABLE OF CONTENTS

Glossary

ACD	allergic contact dermatitis
ACDS	American Contact Dermatitis Society
AE	adverse event
BLA	Biologics Licensing Application
CD	contact dermatitis
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CR	complete response
CRF	Case Report Form
CSR	clinical study report
DIS	Division of Inspections and Surveillance
eCTD	electronic Common Technical Document
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management principles
ICD	irritant contact dermatitis
ICDRG	International Contact Dermatitis Research Group
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IR	information request
ISE	integrated summary of efficacy
MedDRA	Medical Dictionary for Regulatory Activities
MBT	mercaptobenzothiazole
NACDG	North American Contact Dermatitis Group
OCD	occupational contact dermatitis
PeRC	Pediatric Review Committee
PI	package insert
PREA	Pediatric Research Equity Act

PT	patch test
REMS	risk evaluation and mitigation strategy
RPPT	relevant positive patch test
SAE	serious adverse event
sBLA	supplemental biologics licensing application
TCS	topical corticosteroids

1**.** Executive Summary

SmartPractice Denmark Aps submits a Biologics License Application (BLA) for Rubber Panel Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) TEST, a patch test intended for use in persons 6 years of age and older as an aid in the diagnosis of allergic contact dermatitis (ACD) attributable to rubber additives and chemicals . The Rubber Panel T.R.U.E. TEST contains one adhesive panel consisting of 5 allergen patches (Black Rubber mix, 0.075mg/cm^2; Carba mix, 0.25 mg/cm^2; Mercapto mix, 0.075 mg/cm^2; Mercaptobenzothiazole, 0.075 mg/cm^2; and Thiuram mix, 0.025 mg/cm^2). These 5 rubber allergens are included in the Legacy Product T.R.U.E. TEST panels, licensed in 1994 under STN 103738. The Applicant has reconfigured these 5 rubber allergens, without any formulation changes, into the Rubber Panel T.R.U.E. TEST within 2 columns of 3 patches (Patch 2-Carba mix; Patch 3-Black Rubber mix; Patch 4-Mercaptobenzo-thiazole; Patch 5-Mercapto mix; Patch 6-Thiuram mix; Patch 1-negative control, (b) (4)).

To support this BLA, the Applicant submits 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 (97.1%), ICD (25.5%), and atopic dermatitis (53.9%). All enrolled subjects had placement of 3 licensed T.R.U.E. TEST panels 1.1, 2.1, and 3.1 on the back or upper arm (Visit 1). Panel 1.1 contained the negative control (uncoated polyester patch) and Panel 2.1 contained the 5 patches of rubber allergens. Of the 102 subjects, 101 subjects presented 2 days later for patch removal and assessment of panel adhesion and tolerability. Test site reactions were evaluated at 3 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% to Black rubber mix, Mercaptobenzothiazole, and Mercapto mix. One subject had a positive reaction to Thiuram mix 7 days after patch application.

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. Seven of the 44 dermatitis flares reported for all 28 allergens were attributable to a rubber allergen. 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.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) applications submitted to support a new indication trigger pediatric assessment. We supported a partial waiver of the pediatric study requirement from birth to < 6 years of age because it would be impossible or highly impracticable to conduct a trial in subjects under the age of 6 years using the Rubber Panel T.R.U.E. TEST since it is unlikely that infants and children in this age group with ACD would be tested for sensitivity to only one or more of the 5 rubber allergens contained in the proposed product. Rubber allergens are not recognized to be among the common contact allergens among infants and young

children under 6 years of age.The data from Mekos 07 29P1/2/3 401 support the safety and efficacy of the Rubber Panel T.R.U.E. TEST panel for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 6 years of age and older. Therefore, we recommend the approval of this BLA for the proposed indication. Clinical correlation is needed to confirm the clinical relevance of positive results to the Rubber Panel T.R.U.E. TEST panel allergens.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The mean and median age of the 102 subjects (6-17y) enrolled in the trial was 11.6 years and 11 years, respectively. Age representation was evenly distributed across the eligible age range; 45 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%). This population was too small to conduct a meaningful subgroup analysis of safety/efficacy by age, race, or sex.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

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. Current epidemiological estimates suggest that ACD occurs in adults and adolescents at similar rates, specifically 20% and 15% respectively (1, 2). A number of studies suggest that ACD is more common in children 6 years of age and older than previously assumed (2, 3).

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 ICD from ACD. Patch testing is used as an aid to the diagnosis of ACD (3, 4). The 2015 update to the 2006 Practice Parameters on Contact Dermatitis emphasizes the importance of patch testing in the evaluation of suspected ACD, which should be on the differential for any pruritic and eczematous rash that is persistent or chronic. In addition, it states that ICD and ACD are significant clinical problems in the pediatric population, and endorses patch testing in children to confirm diagnosis of the latter, because the two entities are managed differently (1).

Patch testing can be conducted with licensed ready-to-use patch kits, such as T.R.U.E. TEST. Patch testing involves sustained physical contact of suspected or common allergens to the skin of the subject, typically for 48 hours, to allow time for memory T cells to be recruited to the test site. The dermatitis distribution and exposure history can guide the selection of contact allergens for patch testing.

ACD due to rubber is distinct from latex hypersensitivity. Latex hypersensitivity is an IgE-mediated systemic allergy to the proteins contained within the milky sap of the rubber tree. Rubber-containing products contain a range of chemicals intended to convert natural rubber into more durable polymers (5). The contact allergens are the residues of

chemicals used in manufacturing a rubber product, which is a complex process called vulcanization. Thiurams, dithiocarbamates, and mercaptobenzothiazoles are vulcanization accelerators that can act as contact allergens (5,6). The 5 Rubber Panel T.R.U.E. Test allergens are ubiquitous chemicals used in rubber manufacturing that can act as T cell antigens. For children and adults alike, rubber allergens are among the specific relevant allergens to consider when the distribution of the dermatitis includes the lower legs and feet/soles(1).

2.2 Safety and Efficacy of Pharmacologically Related Products

The most common adverse reactions with the licensed T.R.U.E. TEST, which consists of 35 contact allergens and 1 negative control contained within 3 panels (occurring in more than 1% of the study population)), were burning, tape irritation, persistent reactions, erythema, and hyper/hypo pigmentation. Subjects' adverse reactions were recorded on case report forms by study personnel. Adverse reactions were recorded during subject follow-up visits, which varied between 24 and/or 96 hours and/or Day 21.

According to the review by Dr. Patricia Rohan (Division of Epidemiology, CBER, FDA), on the most recent periodic AE report for T.R.U.E. TEST (December 1, 2013, through November 30, 2014), a total of (b) (4) tests were reported sold in the US and a total of 102 adverse event reports (five classified as serious) have been submitted in association with the T.R.U.E. TEST products marketed over the last 20 years (8). Surveillance for potential and possible adverse reactions, namely anaphylaxis and neosensitization, has yielded 15 postmarketing reports of suspected anaphylaxis and 8 cases of possible neosensitization. However, no specific allergens have been implicated.

The efficacy data of T.R.U.E. TEST allergens vary by allergen, ranging from 1.4% (for potassium dichromate and epoxy resin) to as high as 26.1% (for nickel sulfate). In addition, allergens that were added to the legacy product through efficacy supplements have sensitivity, specificity, and concordance data based on the evaluation of confirmed sensitive subjects and reference allergens as positive controls.

2.3 Previous Human Experience with the Product (Including Foreign Experience)

With respect to the rubber allergens contained in the T.R.U.E. TEST, no significant safety concerns have been reported (8).

For this BLA, the data to support the adult indication for the Rubber Panel T.R.U.E. TEST come from 5 of the 10 clinical trials which evaluated the same 5 rubber allergens in the context of the currently-licensed T.R.U.E. Test (7). These trials were conducted in North American and Europe in a total of 466 adults who were patch tested to at least 1 of the 5 rubber allergens (Table 1). 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 ranged from 1.7% (Black Rubber mix) to 4.1% (Thiuram mix).

Table 1: Overview of Clinical Studies Using Rubber T.R.U.E. TEST Allergens Among Adults 18 Years of Age and Older

Clinical Study Overview	Study 1	Study 2	Study 3	Study 4	Study 5	Total
N	127	121	119	50	49	466
Age Range (years)	19-79	18-77	19-76	19-82	18-68	18-82
Sex (% female)	68%	68%	73%	72%	98%	72%
Ethnicity: Caucasian	86%	88%	83%	92%	98%	87%
Ethnicity: Black	9%	12%	11%	4%	0%	12%
Ethnicity: Other	5%	1%	6%	4%	2%	1%
Rubber Carba mix		X	X	X		
Rubber Black rubber mix		X	X	X		
Rubber Mercapto Mix		X	X	X		
Rubber Thiuram Mix	X		X	X	X	
Rubber Mercaptobenzothiazole		X	X	X		

Source: T.R.U.E. TEST PI, Table 1

2.4 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The Rubber Panel T.R.U.E. TEST is a reconfiguration, as described in the Executive Summary and in Section 6.1.4 of 5 rubber chemicals derived from the licensed T.R.U.E. TEST, which is a ready-to-use patch test. T.R.U.E. TEST was licensed in 1994 for use as a diagnostic aid for allergic contact dermatitis in persons 18 years of age and older. The Rubber Panel was first submitted as a supplement to the T.R.U.E. TEST BLA (STN103738/5031) on January 5, 2006 and received on January 9, 2006. Due to CMC issues, CBER issued the first Complete Response (CR) Letter on June 30, 2006 and the Applicant (formerly Mekos Laboratories AS; company name change to SmartPractice Denmark ApS accepted on February 8, 2013, STN 103738/5098) responded on August 14, 2006. On February 12, 2007, CBER issued a second CR letter due to unresolved CMC issues and lack of a proposed plan to fulfill Pediatric Research and Equity Act (PREA) requirements. On August 19, 2014, SmartPractice Denmark AS responded to the second CR letter. Due to significant deficiencies in clinical sections, including the lack of a clinical study report, lack of electronic data sets, a package insert that did not reflect the new indication, and lack of a pharmacovigilance plan, CBER issued a third CR letter on January 12, 2015. The Applicant's response was received on August 26, 2015, and was assessed to be adequate for review.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was not adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. A complete review was accomplished after reviewing the Applicant's responses submitted as 3 amendments to STN 125579.

Reviewer comment: *Of the 1095 pages submitted as the Final Clinical Study Report, 532 pages of an unrelated Phase 3 protocol were inserted in the middle of this submission, beginning on page 386.The pagination was not consecutive, which made this submission difficult to review.*

3.2 Compliance With Good Clinical Practices And Submission Integrity

Bioresearch monitoring (BIMO) inspection of the 1 domestic clinical study site included a data audit of the safety and efficacy results from 65% of study enrollees. No discrepancies were observed between the source documents and data submitted. The inspection did not reveal significant problems that impact the data submitted in this BLA. Problems identified, such as lack of documentation of investigational product accountability, were noted as few and minor by the FDA Investigator. For additional details, please see memorandum by Colonious King, Consumer Safety Officer, Bioresearch Monitoring Branch, FDA.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Mekos 07 29P1/2/3 401		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 2		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Of note the Applicant disclosed (b) (4) as a Consultant from 2000 to 2015. During these 15 years, he received total income of (b) (4), (b) (6) (current exchange of (b) (4), (b) (6) USD) for services that included consultation regarding (1) adverse events involving the product; (2) allergen selection; (3) allergen concentration; (4) changes in

patch testing technique, as well as attendance of seminars and meetings intended for educational development.

Reviewer comment*: The financial information provided does not raise concern regarding the integrity of the study conduct.* (b) (4) *was not an investigator in the study.*

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

At the time of original submission in 2006, there were concerns about the validity of expiration dating of the Rubber Panel T.R.U.E. TEST because of the lack of real-time stability data of the new product. Five product issues were identified during the review of the submission and were communicated to the Applicant in 4 separate IRs. All questions were adequately addressed in the Applicant's responses. Details on the raw materials and the stability and lot release results of the final product were reviewed and found to be acceptable. Please refer to CMC review completed by Dr. Taruna Khurana (Division of Bacterial, Parasitic, and Allergenic Products, CBER, FDA).

The revised lot release protocol template submitted in amendment 125579.013 was determined to be acceptable for use. Confirmatory microbiological testing and chemical assay results of the Rubber Panel T.R.U.E. TEST met specifications for safety and purity as well as potency and identity. Please refer to the 2 reviews by Dr. Karen Campbell (Division of Biologic Standards and Quality Control, CBER, FDA).

4.2 Clinical Pharmacology

4.2.1 Mechanism of Action

A positive response to the patch test is a classic delayed cell-mediated hypersensitivity reaction (type IV), which normally appears within 9 to 96 hours after exposure. Following primary contact, an allergen penetrates the skin and binds covalently or noncovalently to epidermal Langerhans cells. The processed allergen is presented to sensitized helper T-lymphocytes, resulting in inflammation that produces a papular, vesicular, or bullous response with erythema and itching at the site of application (7)

4.3 Statistical

The study results were verified by the statistical reviewer. This open label study did not have any pre-specified criteria for efficacy. Please refer to the statistical review completed by Dr. Ghideon Solomon (Division of Biostatistics, CBER, FDA).

4.4 Pharmacovigilance

Routine pharmacovigilance is recommended. For additional details, please see the review by Dr. Patricia Rohan (Division of Epidemiology, CBER, FDA).

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The review strategy was to focus on safety and efficacy data specific to the rubber allergens. The only exceptions were safety endpoints of panel adhesion and tape-related irritation that were related to the adhesive and excipient components, not the allergen patches, on the product. In addition, relevant adult data from the T.R.U.E. TEST package insert was reviewed (7). Sections 7 (Integrated Overview of Efficacy) and 8 (Integrated Overview of Safety) were eliminated from the review because they were not applicable. The following non-applicable sections were also deleted: 4.2 Assay Validation; 4.3- Nonclinical Pharmacology and Toxicology; 4.4.2- Human Pharmacodynamics (PD); 4.4.3- Human Pharmacokinetics (PK); 5.4-Consultations; 6.1.11.5 -Exploratory and Post Hoc Analyses; 6.1.12.5- Adverse Events of Special Interest; 6.1.12.6-Clinical Test Results; and 9.2- Aspects of the Clinical Evaluation Not Previously Covered.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The Final Clinical Study Report (CSR) for Protocol Mekos 07 29P1/2/3 401, pertinent case report tabulations and forms (module 5), and labeling (module 1)) were reviewed from 125579/000. Missing components (financial disclosure and debarment forms) and additional data were requested through 3 IRs. The Applicant was asked to provide rubber-specific safety and efficacy data from the Mekos study and the adult studies that evaluated any of the 5 Rubber Allergen T.R.U.E. TEST allergens. Applicants' responses (125579/012 (October 21, 2015); 125579/014 (December 3, 2015); 125579/015 (January 15, 2016)) were reviewed and found to be adequate. Positive patch test reactions specific to Rubber Panel T.R.U.E. TEST allergens and data on panel adhesion and tape irritation from T.R.U.E. TEST from 466 adults in 5 clinical trials were reviewed from the Rubber Panel T.R.U.E. TEST draft label and the T.R.U.E. TEST package insert (7).

5.3 Table of Studies/Clinical Trials

The BLA submission includes 1 clinical study (Table 2).

Table 2: Tabular Listing of Clinical Studies in Support of STN 125579

Study	Objectives	Study Design	Test Products, Dosage Regimen, Route of Administration	Number of Subjects	Country	Subjects
Mekos 07 29P1/ 2/3 401	Diagnostic performance of allergens (primary) and safety (secondary)	Open, prospective, single-center	Epicu-taneous patch test T.R.U.E. TEST panels 1.1, 2.1, 3.1	102	USA	Healthy children and adolescents between the ages of 6 and 17 years with suspected ACD

5.4 Literature Reviewed

(1)Fonacier L, Bernstein DI, Pacheco K, Holness DL, Blessing-Moore J, Khan D, Lang D, Nicklas R, Oppenheimer J, Portnoy J, Randolph C, Schuller D, Spector S, Tilles S, Wallace D. Contact dermatitis: a practice parameter-Update 2015. J Allergy Clin Immunol Pract. 2015; 3(3 Suppl): S1-39.

(2)Goldenberg A, Silverberg N, Silverberg J, Treat J, Jacob S. Pediatric Allergic Contact Dermatitis: Lessons for Better Care. J Allergy Clin Immunol 2015; 661-667.

(3)Zug, KA, McGinley-Smith D, Warshaw EM et al. Contact Allergy in Children Referred for Patch Testing: North American Contact Dermatitis Group Data, 2001-2004. Arch Dermatol Vol 2008; 144 (10): 1329-1336

(4)Bernstein DI. Contact Dermatitis for the Practicing Allergist. J Allergy Clin Immunol Prac. 2015; 3(5): 652-658.

(5)Bergendorff O, Persson C, Ludtke A, and Hansson C. Chemical changes in rubber allergens during vulcanization. Contact Dermatitis 2007; 57 (3): 152-157.

(6)Hansson C, Pontén A, Svedman C, Bergendorff O. Reaction profile in patch testing with allergens formed during vulcanization of rubber. Contact Dermatitis 2014; 70 (5): 300-8.

(7)T.R.U.E. TEST [package insert]. SmartPractice Denmark ApS, Hillerod, Denmark. http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM294327.pdf. Accessed February 1, 2016.

(8)Rohan, Patricia (MD, Medical Officer, OBE/Division of Epidemiology, Pharmacovigilance Branch). Pharmacovigilance Plan Review of BLA 125579.0. Dated December 8, 2015.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

Mekos 07 29P1/2/3 401: Clinical Evaluation of T.R.U.E. TEST Panel 1.1, 2.1, and 3.1 in Children and Adolescents

This study is an open-label single-site Phase 3 trial of the 5 rubber chemicals and 24 other test agents included in the T.R.U.E. TEST panels 1.1, 2.1, and 3.1 in pediatric subjects between 6 and 18 years of age (n=102) with suspected ACD. Trial enrollment began in December 2008 through October 2009, and the report was completed on March 11, 2011.

The first subject was enrolled on December 9, 2008. The last subject exited the study on October 27, 2009.

6.1.1 Objectives

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 secondary objective was to describe the safety of the T.R.U.E. TEST Panel 1.1, 2.1, and 3.1 allergens.

Reviewer comment*: CBER agreed that clinical data from testing with the licensed panels would support licensure of the Rubber T.R.U.E. TEST panel because the 5 rubber allergens are included in Panel 2.1 (see Table 3).*

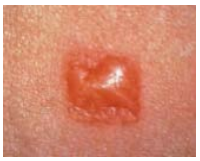
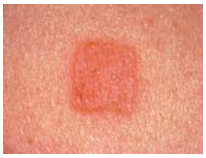
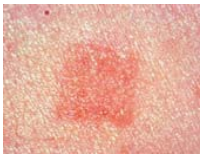
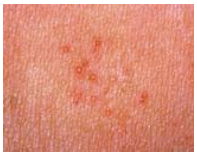
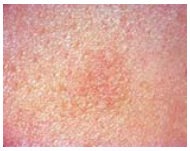
6.1.2 Design Overview

The trial is an observational, open-label, single site trial of 102 pediatric subjects (6 years to 17 years of age) with suspected ACD of patch testing to the 28 contact allergens contained within the 3 licensed T.R.U.E. TEST panels (1.1, 2.1, and 3.1). The 5 rubber allergens on Panel 2.1 and the negative control is on Panel 1.1.

Reviewer comment: *Although the study is an open-label study design, there is an internal negative control patch in T.R.U.E. TEST, which precludes the need for a panel of multiple negative controls. The rubber allergens were part of the original product that was licensed based on percentage of consecutive subjects with positive reactions to patch testing with rubber allergens. Therefore, the study design of the Mekos protocol was agreed upon prior to 2006 at the time of the original submission of the application based on the standards for safety and effectiveness defined by CBER at that time. Since 2006, the Applicant has been required to incorporate positive controls into studies of new allergens to generate sensitivity, specificity, and concordance data with the Finn Chambers and/or sensitivity data from enrolling confirmed positive control subjects to support licensure. Please refer to Section 11.4 for additional discussion of why the data submitted in this application support licensure.*

Prior to Day 0 (Visit 1), eligible subjects completed informed consent/assent and a medical history and exam, with documentation of present and location of any dermatitis sites, results of any previous patch tests in the preceding 5 years. Dermatitis sites were re-examined on Day 0 (Visit 1). All female subjects 15 years of age and older (or with onset of menarche) had to have a negative urine pregnancy test prior to the application of the three T.R.U.E. TEST panels. Two days later (Visit 2), panel adhesion was assessed prior to removal. After 20 minutes, the test sites were evaluated. Subject reports of pruritus and/or burning at test site locations were solicited and corresponding locations were documented. Formal interpretation of test site reactions based on ICDRG guidelines (see Figure 1) were performed at Day 3 or 4 (Visit 3), Day 7 (Visit 4), and Day 21 (Visit 5).

Figure 1: Skin Reaction Scoring Guidelines for Patch Testing

Extreme positive (+++)	Strong positive (++)	Weak positive (+)	Irritant (IR)	Doubtful (?/+)
				
Coalescing vesicles, bullous reaction	Erythema, papules, infiltration, discrete vesicles	Erythema, infiltration, discrete papules	Discrete, patchy, follicular, or homogenous erythema with no infiltration	Faint macular or homogenous erythema with no infiltration

Source: CSR, Figure 9-1 (Section 9.5.1.1 (Efficacy Variables), page 29)

Safety monitoring began on Day 2 (Visit 2) and through Day 21 (Visit 5). Late and/or persistent reactions (at Visit 5) were documented. Photographs were taken at Visit 1 (of test sites and any areas of active dermatitis), Visits 2 and 3 (of all non-negative test site reactions), and Visits 4 and 5 (of any late and/or persistent skin reactions). Each subject was followed for over 21 days, with up to 5 clinical visits. Visit 5 could be substituted with a phone interview.

Reviewer comment: *SmartPractice's request to extend the indication of their Rubber Panel product addresses a need for children to be adequately evaluated for ACD, as identified in the Practice Parameters. This is an unmet need supported by the pediatric ACD literature (2).*

6.1.3 Population

Inclusion criteria included healthy children and adolescents between the ages of 6 years and less than 18 years old with suspected ACD. Exclusion criteria included topical or systemic corticosteroids and immunosuppressants within 1 week on or near the test area, exposure to ultraviolet light, tanning, exposure to investigational drugs or devices or participation in another clinical trial within the 3 preceding weeks, dermatitis affecting the sites for patch placement (back and/or upper arms), unwillingness to comply with activity restrictions required for PT, and unable or unwilling to comply with the multiple clinic visits.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The Rubber Panel T.R.U.E. TEST is a reconfiguration of the 5 rubber allergens and 1 negative control contained in the licensed T.R.U.E. TEST into a smaller panel comprised of 2 columns of 3 patches: (Patch 1-Negative control, (b) (4) ; Patch 2-Carba mix; Patch 3-Black Rubber mix; Patch 4-Mercaptobenzothiazole; Patch 5-Mercapto mix; Patch 6-Thiuram mix). In the version of T.R.U.E. TEST current to the time of this review in 2016, the 5 rubber allergens are distributed within Panels 2.3 (Patch 15- Carba mix; Patch 16-Black Rubber mix; Patch 22- Mercapto mix; Patch 24-Thiuram mix) and 3.3 (Patch 32-Mercaptobenzothiazole).

The Mekos trial supporting this BLA for the Rubber Panel T.R.U.E. TEST evaluated an earlier version of T.R.U.E. TEST- Panels 1.1, 2.1, and 3.1- current at the time of the conduct of the study in 2008. Panel 2.1 contained the 5 rubber allergens (Carba mix - ; Black Rubber mix; Mercapto mix; Thiuram mix- and Panel 1.1 contained the negative control. Three adhesive panels were applied to the back and/or upper arm of the 102 children and adolescents. After 2 days, each subject had this removed in the clinic. The sites were evaluated at 3 time points, starting on Day 3 and out to Day 21

Reviewer comment*: The use of the licensed T.R.U.E. TEST product was accepted prior to the submission of this BLA because the formulations of the rubber allergens are unchanged. To ascertain product stability, the Applicant submitted raw material, final product stability and lot release specification data from the Rubber Panel T.R.U.E. TEST.*

6.1.5 Directions for Use

The adhesive panel of allergens is placed on healthy skin of the back. Panels are removed and the skin is evaluated 48 and 72-96 hours after application (7).

6.1.6 Sites and Centers

This trial was conducted at a single site – Rady Children's Hospital (San Diego, CA) and had 2 site investigators (Sharon Jacob, MD and Lawrence Eichenfield, MD).

6.1.7 Surveillance/Monitoring

Subjects were followed for 21 days after enrollment (Table 3). Following patch placement on Day 0 (Visit 1), subjects returned on Day 2 for panel evaluation and removal (Visit 2). Panel adhesion, termed "compliance," was evaluated and characterized using a 5-point scale based on degree of skin-to-panel contact and tape edge adherence. Panels with good skin contact and all edges adherent were graded as excellent. Those with "acceptable" skin contact with loosening observed in some areas of the tape were graded as good. Fair adhesion indicated variable skin-to-panel contact with lifting observed at tape edges. Poor adhesion indicated little to no skin contact with the panel. The lowest grade was if 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.

Reviewer comment: *This safety monitoring plan is the same as what was done for the adult trials for T.R.U.E. TEST and is consistent with current patch testing guidelines(1).*

Table 3: Study Procedures

Procedure	Visit 1[a] (Day 0)	Visit 2 (2 days after Visit 1)	Visit 3[b] (3 to 4 days after Visit 1)	Visit 4 (7 days after Visit 1)	Visit 5[c] (21 days after Visit 1)
Informed Consent/HIPAA	X				

Procedure	Visit 1[a] (Day 0)	Visit 2 (2 days after Visit 1)	Visit 3[b] (3 to 4 days after Visit 1)	Visit 4 (7 days after Visit 1)	Visit 5[c] (21 days after Visit 1)
Inclusion/Exclusion	X				
Demographics	X				
Prior patch test result	X				
Pregnancy test[d]	X				
Current evidence of contact dermatitis	X				
Apply patches	X				
Remove patches[e]		X			
Record tape irritation and itching/burning		X			
Record skin reactions		X[f]	X	X	X
Photograph test sites		X	X	X	X[g]
Record AEs		X	X	X	X

Source: Adapted from STN 125579 CSR, Table 9-1, p. 28
AE=adverse event; HIPAA=Health Insurance Portability and Accountability Act; Screen=screening visit

[a] May have occurred prior to or at the same time as Visit 1
[b] Visit 3b may have been conducted 4 days after Visit 1 (+1 day) at the investigator's discretion
[c] May have been conducted via telephone at the investigator's discretion if no late or persistent skin reactions were present.
[d] To be performed for female subjects 15-18 years of age, inclusive (or with onset of menarche)
[e] Prior to removing the patches, investigators inspected the integrity of the patches and recorded any apparent loss of skin contact.
[f] Before investigators evaluated skin reactions after patch removal, the skin was allowed to rest for 20 minutes.
[g] Not done if the subject had no late or persistent skin reactions and participated via telephone.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint of diagnostic performance was the frequency of positive reactions, as defined by the ICDRG guidelines, to each of the 5 rubber allergens. Secondary endpoints of safety include standard reporting of frequencies of AEs and serious AEs and product-specific parameters of late and/or persistent reactions (diagnosed at Day 21 after patch application), tape-induced irritation at each test site upon patch removal, incomplete panel adhesion, and subject-reporting of pruritus or burning during the 48 hours that the T.R.U.E. TEST panels were affixed to skin. Based on the CSR, there were no modifications of study endpoints during or after completion. There were no pre-specified criteria for study success.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The sample size of 100 can detect an increase in adverse events from 7.6% (based on data from the licensed T.R.U.E. TEST in adults) to 15.6% (in the present study with T.R.U.E. TEST in children and adolescents) with a power of 80% and a significance level of 0.05 using a one-sided test of the null hypothesis, which is that Pe (new allergen) = Pc (historical control). No imputations were made for missing data. No adjustments were made for multiple comparisons. Absolute numbers, frequencies, and 95% confidence intervals of positive, negative, irritant, and doubtful reactions were presented for each of the 28 allergens at 3 time points after panel application: 3 to 4 days, 7 days, and 21 days. Secondary endpoints from the 3 licensed panels, which include the 5 rubber allergens, were analyzed descriptively. Safety data included overall frequencies of subjects with AEs, breakdown of AEs by grade, causality assignment, need for intervention. Frequencies of tape irritation, panel adhesion, and late and

persistent skin reactions were summarized according to the pre-specified severity classification. Subpopulation analyses based on demographics were also performed.

Reviewer comment*: The safety endpoints are descriptive and the size of the safety database is adequate based on the experience in adults with the licensed T.R.U.E. TEST product that contains the rubber allergens. In terms of efficacy, the study is not powered based on pre-specified criteria for success; hence 95% confidence intervals have limited utility in this study. Please see reviewer comment in Section 6.1.2 for discussion on study design.*

6.1.10 Study Population and Disposition

One hundred and two subjects (6 to 17 years old) were enrolled at one investigational site. Two subjects dropped out; one withdrew consent 1 day after patch application and the other subject was lost to follow-up. No subjects had reapplication of panels after Day 0 (Visit 1).

6.1.10.1 Populations Enrolled/Analyzed

All 102 subjects enrolled were analyzed for demographics. One hundred and one subjects were evaluated at Visit 2 for panel adhesion, panel removal, and local inspection for tape-related irritation. Up to 101 subjects presented for patch site reading on Visits 3 (n=101) and 4 (n=96). No significant protocol deviations, specifically missing 2 or more clinic visits, were reported for the 100 subjects who completed the protocol. Table 4 presents the numbers of subjects presenting to each of the 5 visits of the protocol.

Table 4: Children and Adolescents 6 to 17 Years of Age Presenting for Each of the 5 Clinic Visits in Protocol Mekos 07 29P1/2/3 401

Day	Visit	N
0	1	102
2	2	101
3 or 4	3	101
7	4	96 *
21	5	100

*Among the 5 subjects who did not present for Visit 4 (Subject 009, 054, 055, 058, and 083), none had positive, doubtful, or irritant reactions to the 5 rubber allergens. Four of the 5 had positive reactions to other contact allergens, and 1 subject had no positive reactions to panels 1.1, 2.1, and 3.1 at Visit 3.

6.1.10.1.1 Demographics

Age representation of the 102 subjects (mean age 11.6 years) was evenly distributed across the eligible age range; 45 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%). Of the 101 subjects who presented to Visit 3 and the 96 subjects who presented to Visit 4, 17 subjects had a positive reaction to at least 1 of the 5 rubber allergens. This population was too small to conduct a meaningful subgroup analyses of safety or efficacy by age, race, or sex.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Among the 102 subjects who enrolled (mean age of 11.6 years), 101 had active dermatitis, with variable distribution. Seventy-four subjects had dermatitis affecting the legs and/or feet (73.3%), 69 subjects had dermatitis affecting the arms and/or hands (68.3%), 48 (47.5) had dermatitis of the face and/or scalp and/or neck, and 42 (41.6%) had truncal involvement. Most of the subjects had a history of ACD (97.1%) and ICD (25.5%), as well as atopic dermatitis (53.9%). As expected, none had occupational dermatitis.

Reviewer comment: *The majority of subjects (n=74; 73.3%) had dermatitis involving the lower legs and/or feet. Although individuals with rubber exposure histories were not specifically included in this study, patch testing to rubber allergens is recommended for children and adults with lower leg and foot dermatitis (1).*

6.1.10.1.3 Subject Disposition

All 102 subjects underwent patch testing. 101 wore the patch for the pre-specified duration of 2 days and had adhesion and test site burning and pruritus formally evaluated at Visit 2. 101 subjects presented for test site reading at Visits 3 and 96 presented for test site reading at Visit 4. Two subjects withdrew from the study.

6.1.11 Efficacy Analyses

The primary endpoint was the frequency and characterization of a reaction to each allergen. Skin reactions were evaluated based on patch testing guidelines established by the International Contact Dermatitis Research Group (ICDRG) published in 1970 (Figure 1).

Reviewer comment: *The ICDRG system continues to be widely used and is accepted as the standard, and formally recommended by the Practice Parameters in Summary Statement. Lack of positive controls and evaluation of the clinical relevance of the positive patch test results in the 100 subjects are limitations of this trial.*

6.1.11.1 Analyses of Primary Endpoint(s)

Positive reactions to Carba and Thiuram mixes were the most frequent at Day 3 or 4, but tended to resolve by Day 7. Irritant reactions to these agents were infrequent (Table 6). Twenty-one of the 100 subjects who completed the protocol had at least 1 non-negative reaction to any of the 5 rubber allergens (Table 5). Of these, 17 subjects had at least 1

positive reaction to any of the 5 rubber allergens. Total frequencies of positive reactions to each of the 5 rubber allergens observed at Visit 3 or 4 in children and adolescents (Table 6) were similar to those reported in adults (Table 7).

Table 5: Rubber Allergen-Specific Reaction Profile of the 21 Subjects with At Least 1 Non-Negative Patch Test Reaction to a Rubber Panel T.R.U.E. TEST Allergen After 3 to 4 Days (Visit 3) or 7 Days (Visit 4) After Patch Application

Positive Reactions SUB ID	Black Rubber Mix Visit 3 N=101	Black Rubber Mix Visit 4 N=96	Carba Mix Visit 3 N=101	Carba Mix Visit 4 N=96	MBT Visit 3 N=101	MBT Visit 4 N=96	Mercapto Mix Visit 3 N=101	Mercapto Mix Visit 4 N=96	Thiuram Mix Visit 3 N=101	Thiuram Mix Visit 4 N=96
TOTAL	2	0	7	1	2	1	2	1	6	1
002									+	?/+
003	+	Neg								
013									+	?/+
015			+	Neg						
023			++	Neg						
031			++	Neg						
035	?/+	Neg								
038									+	Neg
044			+	Neg						
046			+	Neg					+	Neg
047									+	Neg
048			+	++						
051			+	Neg						
063					++	+	++	+		
076	?/+	Neg								
080									+	?/+
081	Neg	?/+			+	Neg				
092									IR	?/+
095	+	Neg								
098			?/+	Neg			+	?/+	?/+	+
102									?/+	Neg

MBT=Mercaptobenzothiazole; SUB ID= Subject identification number; Neg=Negative; ?/+=doubtful; IR=irritant

Source: STN 125579 CSR, Line Listing 16.2.6.1, pp. 281-382

Reviewer comment: *The variable profile of positive reactions to each of the 5 rubber allergens suggest that it is unlikely that there is a single rubber allergen to aid in the diagnosis of rubber-induced ACD.*

Table 6: Patch Test Site Reactions[a] in Children and Adolescents at Days 3 to 4 (Visit 3) and Day 7 (Visit 4) After Patch Application

VISIT Number - Test Patch	N	Positive reaction, n (+,++,+++)	Negative reaction, n (Neg)	Irritant reaction, n (IR)	Doubtful reaction, n (?/+)
Visit 3 - Carba mix, 0.25 mg/cm^2	101	7	93	0	1
Visit 3 - Thiuram mix, 0.025 mg/cm^2	101	6	92	1	2
Visit 3 - Black rubber mix, 0.075 mg/cm^2	101	2	97	0	2
Visit 3 - Mercaptobenzothiazole 0.075 mg/cm^2	101	2	99	0	0
Visit 3 - Mercapto mix, 0.075 mg/cm^2	101	2	99	0	0
Visit 4 - Carba mix, 0.25 mg/cm^2	96	1	95	0	0
Visit 4 - Thiuram mix, 0.025 mg/cm^2	96	1	91	0	4
Visit 4 - Black rubber mix, 0.075 mg/cm^2	96	0	95	0	1
Visit 4 - Mercaptobenzothiazole 0.075 mg/cm^2	96	1	95	0	0
Visit 4 - Mercapto mix, 0.075 mg/cm^2	96	1	94	0	1

[a]Skin reactions were evaluated based on patch testing guidelines established by the International Contact Dermatitis Research Group (ICDRG)

Source: Tabulated from review of Line Listing 16.2.6.1 in STN 125579 CSR, pp. 281-382

Reviewer comment: *The study did not evaluate how many of the positive reactions were relevant positive patch tests (RPPTs) as defined by the Practice Parameter. Assessment of RPPTs is based on follow up and clinical assessment of subjects with positive patch tests results to determine if results from patch testing. Due to the uncertainties regarding the effectiveness of the Rubber Panel T.R.U.E. TEST, the indication for the Rubber Panel T.R.U.E. TEST indicates that it is approved for use as an aid to the diagnosis of rubber allergy. The use of this product requires clinical correlation. The data support this indication because of the low frequency of irritant and doubtful reactions. The majority of positive reactions occurred at Day 3 or 4 after patch application. The low overall frequency (1 to 4%) of positive reactions to rubber allergens is consistent with the epidemiology of rubber-related ACD in adults (Table 7).*

Table 7. Frequencies of Positive Reactions to Rubber Panel T.R.U.E. TEST Allergens in Adults

Visits 3 and 4 (cumulative)	Subjects N	Positive reactions n **(%)**
Carba mix	290 [2,3,4]	6 **(2.1)**
Black Rubber mix	290 [2, 3, 4]	4 **(13.8)**
Mercapto Mix	290 [2, 3, 4]	8 **(2.8)**
Thiuram mix	345 [1, 3, 4, 5]	18 **(5.2)**
Mercaptobenzothiazole	290 [2 ,3 ,4]	8 **(2.8)**

* Relevant studies 1,2,3,4,9 that included testing with at least 1 of the 5 Rubber Panel T.R.U.E. TEST allergens cited in T.R.U.E. TEST package insert (7)

Source: Applicant's January 14, 2016 response to Information Request dated December 11, 2015.

Reviewer comment: *Errors in the positive reaction frequencies for black rubber mix (5/290 to 4/290) and mercapto mix (9/290 to 8/290) were brought to our attention by the Applicant. A doubtful reaction for each of these 2 allergens was miscategorized as a positive reaction, and this was verified by original data. The Applicant submitted the Clinical Study Report for Study 4 on May 10, 2016. Evidence of miscategorization was noted on page 63 of the submission. These 2 corrections are reflected in the label. The Applicant will be notified that these 2 edits must also be made for T.R.U.E. TEST, and that a labeling supplement should be submitted to STN 103738.*

6.1.11.2 Subpopulation Analyses

Seventeen of the 101 subjects had positive reactions to at least one of the 5 rubber allergens detected 3 to 4 days after patch application or 7 days after patch application (Visits 3 and 4). Table 8 presents the distribution of the positive reactions to each of the rubber allergens by age categories (children (6-12 year olds), and adolescents (13-18 year olds)), sex, and race (Caucasian and non-Caucasian).

Table 8: Frequency of Positive Reactions to the Rubber Panel T.R.U.E. TEST Allergens by Age, Sex, and Race in Children and Adolescents at Days 3-4

Rubber Panel T.R.U.E. TEST Allergen	Total subjects (N=101)	Age 6-12 years (N=56)	Age 13-17 years (N=45)	Sex Males (N=49)	Sex Females (N=52)	Race Caucasian (N=40)	Race Non-Caucasian (N=61)
Carba Mix	7[a]	4	3	3	4	1	6
Thiuram Mix	6[a]	1	5	4	2	4	2
Black Rubber mix	2	2	0	2	0	1	1

Rubber Panel T.R.U.E. TEST Allergen	Total subjects (N=101)	Age 6-12 years (N=56)	Age 13-17 years (N=45)	Sex Males (N=49)	Sex Females (N=52)	Race Caucasian (N=40)	Race Non-Caucasian (N=61)
Mercaptobenzothiazole	2[b]	1	1	1	1	1	1
Mercapto Mix	2[b]	0	2	1	1	1	1

Source: Summarized from tables of reaction frequencies by age, sex, and race from STN 125579 CSR, pp.97-111.

[a] Subject 046 had a positive reaction to carba mix and to thiuram mix

[b] Subject 063 had a positive reaction to mercaptobenzothiazole and to mercapto mix

Reviewer comment: *The ability to draw conclusions from the subgroup analyses is limited given the small size of the study.*

6.1.11.3 Dropouts and/or Discontinuations

Two subjects dropped out of the study. One subject withdrew consent and the other was lost to follow-up. The CSR includes line listings that provide additional information on drop-outs. Subject 075 was an 11-year-old Hispanic male who removed the panels on his own after Visit 1 and withdrew consent before Visit 2. He did not present for any subsequent study visits (CSR, p. 972, 969). The second subject who dropped out was a 15-year-old Hispanic female (Subject 035) who was lost to follow-up (CSR, Line Listing 16.2.1.3, p. 926).

Reviewer Comment: *The dropouts/discontinuations did not appear to be attributed to adverse reactions; the number of dropouts was low (approximately 2%). The number of dropouts and discontinuations do not raise concerns regarding the conduct of the study or safety of the product.*

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety analyses of panel adhesion and tape-related irritation are based on the 102 subjects enrolled in the Mekos protocol. No subjects were patch tested twice.

Reviewer Comment: *The safety analysis is focused on adverse reactions to the 5 Rubber Panel T.R.U.E. Test allergens only.*

6.1.12.2 Overview of Adverse Events (AEs)

Evaluation of Poor Adhesion

Of the 102 subjects enrolled, 100 subjects presented for evaluation of adhesion at Visit 2. None of the panels fell off. Rates of poor adhesion (see Section 6.1.7) for Panels 1.1 (containing negative control), 2.1 (containing the 5 rubber allergens), and 3.1 (containing

none of the rubber allergens) were 10%, 9%, and 4%, respectively. Excellent adhesion was observed in most of the pediatric subjects for all 3 panels (72% for Panels 1.1 and 2.1, 82% for Panel 3.1). Good adhesion was the second most frequently reported grading (19% for panels 1.1 and 2.1 and 14% for Panel 3.1).

Evaluation of Panel-Induced Tape Irritation

After removal of Panels 1.1, 2.1, and 3.1, subjects underwent evaluation of objective signs of tape irritation (see Table 9). The majority of subjects (81 to 82%) had none to weak tape irritation at panel sites.

Reviewer comment: *Data on local pruritus and burning were not included in the review because relatedness to the tape versus any of the 28 allergens could not be determined.*

Table 9: Number of Children and Adolescents 6 to 17 Years of Age Observed with Tape Irritation 2 Days After Application of T.R.U.E. TEST

Tape Irritation Grade (N=101)	T.R.U.E. TEST Panel 1.1	T.R.U.E. TEST Panel 2.1	T.R.U.E. TEST Panel 3.1
None	*38*	*37*	*40*
Weak	44	44	41
Moderate	16	16	18
Strong	3	4	2

Source: STN 125579, CSR, Table 12-3, p.57

Evaluation of Solicited AEs

The overall AE frequency of 34.3% was based on 52 AEs (n=50 graded as mild to moderate) from 35 pediatric subjects due to any of the 28 allergens included in Panels 1.1, 2.1, and 3.1. Neither of the 2 severe AEs, one of which was judged to be related to the patch testing, were attributed to the 5 rubber allergens. None of the 7 persistent reactions observed in 4 subjects were associated with rubber allergens.

In response to an IR, the Applicant provided rubber allergen-specific safety data, which include a total of 8 AEs from 102 subjects (Table 10). Based on the case reports and biological plausibility of dermatitis flares at sites distant from patch testing, these AEs were classified as ARs. Rates of AEs with patch testing to a range of common allergens in adults have been estimated at 8.1%. When limited to rubber allergens, the rates are significantly less, ranging from 0.98% to 5.88% (Table 10) for each rubber allergen.

Reviewer comment: *The safety data to support licensure of the Rubber Panel T.R.U.E. TEST BLA is based on an analysis of AEs attributed to the 5 rubber allergens because non-rubber allergens are not contained in this product.*

Direct comparison of the overall AE rate of 34.3% in the 102 children and adolescents from the Mekos study to the historical AE rate of 18% from 8 adult clinical trials is not

ideal due to 2 potential confounders: (1) the high prevalence of atopic dermatitis, which is predominantly a pediatric condition, in the former population, and (2) the lack of surveillance of dermatitis flare in the adult studies. It is more appropriate to view the overall rate of AEs for Rubber Panel T.R.U.E. TEST to be 8% (Table 10).

Ongoing AEs at Visit 5

At Day 21 (Visit 5), 44 of the 102 subjects were documented to have active exacerbation of pre-existing dermatitis. The trial investigators made the clinical decision that none of these subjects needed further follow-up. Reasons for this included the chronicity of the pre-existing dermatoses and the commonly observed occurrence of dermatitis flare with patch testing in children.

Reviewer comment: *Safety information related to dermatitis flares was not collected in the 5 adult clinical trials with the licensed T.R.U.E TEST. In the pediatric study, dermatitis flares were common, which is consistent with the predominance (53.9%) of subjects with concurrent atopic dermatitis. Dermatitis flares can be attributed to the mandatory cessation of chronic topical medications for a minimum of 7 days for accurate patch test results as well as the allergen exposure from the patch test product. Please see Section 10 for further discussion.*

Table 10: Total Adverse Reactions Associated with Rubber Panel T.R.U.E. TEST Allergens in Children and Adolescents Within 21 days After Panel Application

Adverse Event Type	Black Rubber Mix N=102	Carba mix N=102	MBT N=102	Mercapto mix N=102	Thiuram mix N=102	Neg Control N=102
Adverse Events n (%)	**1 (0.98%)**	**6 (5.88%)**	**0**	**0**	**1 (0.98%)**	**0**
Erythema	0	0	0	0	0	0
Dermatitis Flare Distant to Panel Sites	1 (0.98%)	5 (4.90%)	0	0	1 (0.98%)	0
Dermatitis - Mild	1 (0.98%)	4 (3.92%)	0	0	1 (0.98%)	0
Dermatitis - Moderate	0	1 (0.98%)	0	0	0	0
Rash due to coalescence of positive reactions from adjacent patches	0	1 (0.98%)	0	0	0	0
Rash – Mild	0	1 (0.98%)	0	0	0	0
Hyperpigmentation	0	0	0	0	0	0
Pruritus	0	0	0	0	0	0

Adverse Event Type	Black Rubber Mix N=102	Carba mix N=102	MBT N=102	Mercapto mix N=102	Thiuram mix N=102	Neg Control N=102
Scarring	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0
Delayed Reaction	0	0	0	0	0	0
Sensitization (potential)	0	0	0	0	0	0
Sensitization (probable)	0	0	0	0	0	0
Infiltration/Skin thinning	0	0	0	0	0	0

Source: Adapted from 4 tables submitted on December 3, 2015 by the Applicant in response to an IR emailed on November 11, 2015

Reviewer comment: *Although the more cause of dermatitis flares may be due to withholding of chronic topical medications, such as corticosteroids and calcineurin inhibitors, for 7 days prior to patch testing, dermatitis flares can result from exposure to clinically relevant contact allergens, such as rubber allergens. Hence, we consider these reactions to be possibly related to the patch testing.*

Table 11: Total Adverse Reactions Associated with Rubber Panel T.R.U.E. TEST Allergens in Adults*

Adverse Event Type	Black Rubber mix N=290	Carba mix N=290	MBT N=290	Mercapto mix N=290	Thiuram mixm N=345	Neg Control N=345
Adverse Events n (%)	4 (1.4%)	0	5 (1.7%)	7 (2.4%)	7 (2.0%)	0
Erythema	2 (0.7%)	0	2 (0.7%)	3 (1.0%)	1 (0.3%)	0
Dermatitis Flare	0	0	0	0	0	0
Hyperpigmentation	0	0	2 (0.7%)	3 (1.0%)	2 (0.6%)	0
Pruritus	2 (0.7%)	0	1 (0.3%)	1 (0.3%)	4 (1.2%)	0
Scarring	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0
Rash	0	0	0	0	0	0

Adverse Event Type	Black Rubber mix N=290	Carba mix N=290	MBT N=290	Mercapto mix N=290	Thiuram mixm N=345	Neg Control N=345
Delayed Reaction	0	0	0	0	0	0
Sensitization (potential)	0	0	0	0	0	0
Sensitization (probable)	0	0	0	0	0	0
Infiltration/Skin thinning	0	0	0	0	0	0

**These safety data are derived from 4 of the 5 adult trials (2, 3, 4, and 9) that included evaluation of Rubber Panel T.R.U.E. TEST Allergens.*

Source: From Table 5 of Applicant's response (December 3, 2015) to IR (emailed November 11, 2015)

6.1.12.3 Deaths

No deaths occurred during the 21 days of follow-up per subject.

6.1.12.4 Nonfatal Serious Adverse Events

No nonfatal SAEs occurred during the 21 days of follow-up per subject.

6.1.12.5 Subpopulation Analyses

A subgroup analysis of safety data based on age, sex, and race could not be performed due to the low number of AEs related to the rubber allergens. See Table 11.

6.1.12.6 Dropouts and/or Discontinuations

Reason for the 2 dropouts were provided in the CSR. See Section 6.1.11.4 for details.

6.1.13 Study Summary and Conclusions

Of the 102 subjects enrolled in the Mekos trial, there were a total of 8 mild adverse reactions associated with the Rubber Panel T.R.U.E. TEST allergens. This is comparable to the historical adverse event rate of 8.1% observed in adults following patch testing with T.R.U.E TEST products.

The Mekos trial showed that 17 of the 100 consecutive subjects who completed the protocol had positive reactions to at least one of the 5 rubber agents. The Carba and Thiuram mixes were the most common of the 5 chemicals to induce positive reactions interpreted at Visit 3 (7% and 6%, respectively). All but one of the reactions (to Thiuram) were detected within 3 to 4 days after patch application (Visit 3). The frequencies were similar to what have been described in adults. Meaningful subgroup analyses could not be performed from the 17 subjects because there were no positive controls. The Mekos trial was not designed to confirm the clinical relevance of positive patch test results. Therefore, the data indicate that the Rubber Panel T.R.U.E. TEST is at best, an aid to diagnosis of ACD due to rubber allergens.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Pediatric Use and PREA Considerations

We granted a partial waiver for persons <6 years of age with the rationale that the necessary studies are impossible or highly impracticable because the number of patients with rubber allergy in this age group is small.

9.1.2 Immunocompromised Patients

Immunocompromised participants were excluded from Mekos 07 29P1/2/3 401.

9.1.3 Geriatric Use

Small numbers of subjects 65 years of age and older were included in the 5 adult clinical studies with the licensed T.R.U.E. TEST product (please see Table 1). Geriatric subjects were not included in Mekos 07 29P1/2/3 401.

Reviewer comment: *The number of subjects > 65 years of age was too low to draw any meaningful conclusions regarding the safety or efficacy of Rubber Panel T.R.U.E TEST in this population. The licensed T.R.U.E. TEST panel, which contains the 5 rubber allergens contained in the Rubber Panel T.R.U.E. TEST, is currently approved for use in adults 18 years of age and older based on the same data considered for this BLA.*

10. Conclusions

Study Mekos 07 29P1/2/3 401 was an open-label Phase 3 trial of 28 contact allergens, including 5 allergens contained in the Rubber Panel T.R.U.E. TEST. The study population of 102 pediatric subjects was representative of children and adolescents who would benefit from patch testing. Among the 100 children and adolescents with active dermatitis who completed the protocol, 17 subjects had positive reactions, 4 subjects had doubtful reactions, and 1 subject had an irritant reaction to one or more of the Rubber Panel T.R.U.E. TEST allergens. Positive reactions to each of the 5 rubber allergens ranged as follows: 7% to Carba mix, 6% to Thiuram mix, and 2% to Black rubber mix, Mercaptobenzothia-zole, and Mercapto mix. One subject had a positive reaction to Thiuram mix 7 days after patch application. Doubtful reactions were most common with Thiuram mix (n=6), followed by Black Rubber mix (n=3), and Mercaptobenzothiazole and Carba mix (n=1 for each). The 1 reported irritant reaction was to Thiuram mix.

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 associated with the panels. 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. Seven of the 44 dermatitis flares reported for all 28 allergens were attributable to a rubber allergen. 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.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

A comparison of the risks and benefits of licensure of Rubber Panel T.R.U.E. TEST for use in persons 6 years of age and older is presented in Table 12 and discussed in Section 11.2.

Table 12: Risk-Benefit Considerations for Licensure of Rubber Panel T.R.U.E. TEST

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ACD is a common and chronic condition that affects up to 20% of adults and children. • Patch testing is necessary to confirm the diagnosis of ACD, which has a presentation shared by a number of other dermatoses. History and physical exam do not have sufficient specificity. • Occupational ACD is the most common work compensation-eligible condition.	• Unverified diagnoses of rubber-related occupational ACD prevents affected individuals from proper management, job performance, appropriate modification of the work environment, and possibly due compensation.
Unmet Medical Need	• There are no patch test products currently licensed by the FDA for use in persons younger than 18 years of age. • The 2015 update to the 2006 Practice Parameters on Contact Dermatitis emphasizes the importance of patch testing in the evaluation of suspected ACD, which should be on the differential for any pruritic and eczematous rash that is persistent or chronic. In addition, it states that ICD and ACD are significant clinical problems in the pediatric population, and endorses patch testing in children to distinguish ACD from ICD, because the two entities are managed differently (1).	• Undiagnosed ACD in children hinders adequate management and increases the risk of prolonged exposure to oral and topical immunosuppressants. There are currently no licensed patch testing products for subjects under 18 years of age.
Clinical Benefit	• The 5 rubber allergens contained in the Rubber Panel T.R.U.E. TEST are included in T.R.U.E. TEST panels, licensed since1994. • One clinical trial in children 6 years to 17 years of age was submitted. This was an open-label observational study of 102 consecutive subjects 6-17 years of age. Positive reactions to each of the 5 rubber allergens ranged as follows: 7% to Carba mix, 6% to Thiuram mix, and 2% to Black rubber mix, Mercaptobenzothiazole, and Mercapto mix. One subject had a positive reaction to Thiuram mix 7 days after patch application	• The data support the use of the Rubber Panel T.R.U.E. TEST 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 5 substances included on the Rubber Panel T.R.U.E. TEST.
Risk	• In children and adults, tape irritation was common and rates seen with the panel containing the rubber allergens were. Tape irritation is self-limited and resolved by the time of observation on Day 2 and repeat visit at Day 3 or 4. • Most adverse reactions were mild. • None of the AEs resulted in discontinuation of any subject from the study. • There were no case of anaphylaxis or neosensitization.	• All the evidence indicates that the risk of patch testing with the Rubber Panel T.R.U.E. TEST is minimal.
Risk Management	• The risks of patch testing with Rubber Panel T.R.U.E. TEST allergens in children were related to flaring of pre-existing dermatitis at sites distant from patch test placement. • In contrast to adults, no hyperpigmentation, scarring, or pruritus were attributed to the rubber allergens in children. • No other safety signals were apparent in children and adolescents 6 to 17 years of age.	• Routine measures, such as the package insert and the current pharmacovigilance plan, would be adequate to manage the risks

11.2 Risk-Benefit Summary and 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 that have used T.R.U.E. TEST products. 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 ACD. Rubber Panel T.R.U.E. TEST presents a favorable overall risk-benefit profile.

11.3 Recommendations on Regulatory Actions

The safety and descriptive efficacy data provided in this BLA support the approval of Rubber Panel T.R.U.E. TEST 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 5 substances included on the Rubber Panel T.R.U.E. TEST.

11.4 Labeling Review and Recommendations

Revisions were made to the label based on the data pertaining to the Rubber T.R.U.E. TEST allergens submitted to the BLA. Due to the uncertainties regarding the effectiveness of the Rubber Panel T.R.U.E. TEST, the indication for the Rubber Panel T.R.U.E. TEST states that it is approved for use as an aid to the diagnosis of rubber allergy. The use of this product requires clinical correlation.

Revisions to the label for Rubber Panel T.R.U.E. TEST included the elimination of text regarding sensitivity, specificity, and concordance data because these endpoints were not evaluated for the Rubber Panel T.R.U.E. TEST allergens. Safety and efficacy data were repositioned as necessary so that they werepresented in the appropriate sections of the label. In addition, the Applicant identified erroneous categorization of positive reaction frequencies for 2 of the rubber allergens (black rubber mix and mercapto mix) from Study 4, an open-label multi-center studyevaluating the 5 rubber allergens in 50 adults with suspected ACD. The CSR for Study 4 was submitted on May 10, 2016 as an amendment. This document was reviewed; Table 6 (page 63) illustrates that the original frequencies for positive reactions to black rubber mix and mercapto mix among adults erroneously included macular erythema (which is considered a “doubtful” rather than a “positive” reaction). Table 6 in the label was revised accordingly. The label text was edited for improved clarity and tables supplemented with footnotes to stand alone, without the need to reference other tables or text. The Pregnancy and Lactation Labeling Final Rule did not apply to this BLA since it was submitted prior to June 30, 2015.

11.6 Recommendations on Postmarketing Actions

No safety signals were identified from any source that would trigger a safety postmarketing study as a postmarketing commitment (PMC), a postmarketing requirement (PMR), or a Risk Evaluation and Mitigation Strategy. Routine pharmacovigilance is recommended.