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).*

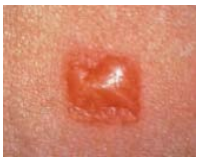
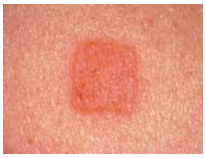
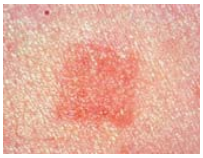
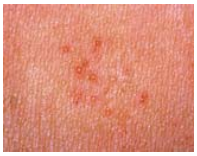
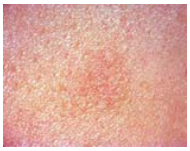
6.1.2 Design Overview

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).

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.