DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Date: February 13, 2012

To: File, STN 103738/5074

From: Ronald L Rabin, MD, Chair, LIB/DBPAP/OVRR

Subject: Summary Basis of Approval Recommendation Memorandum

Through: Wellington Sun, MD, Director, DVRPA/OVRR

Applicant: Mekos Laboratories AS, Herredsvejen 2, 3400 Hillerod, Denmark; (US license 1623)

Products: Multiple Products: Allergen Patch Test Kit®. [T.R.U.E. (Thin-layer Rapid Use Epicutaneous) TEST Allergen Patch Test Kit]

The T.R.U.E. TEST is an epicutaneous patch test, which consists of a set of three panels of allergens, Panel 1.1, 2.1, and 3.1, that are used as an aid in the diagnosis of allergic contact dermatitis. This document addresses the reviews for approval of the following seven new T.R.U.E. TEST allergens for use in adults 18 years of age and older whose history suggests sensitivity to one or more of the substances included on the seven allergens patches.

Table 1. Products approved for inclusion into the T.R.U.E. Test allergen panels.

Product	Vehicle	Conc. (mg/cm2)	Exposure context
Gold sodium thiosulfate (GST)	Hydroxypropyl-cellulose (HPC)	0.075	Jewelry
Hydrocortisone-17-butyrate (H-17-B)	Polyvinylpyrrol-idone (PVP)	0.02	OTC medication
Parthenolide	PVP	0.003	Plant of Compositae family
Methyldibromoglutaronitrile (MDBGN)	PVP	0.0055	Cosmetic preservative
Bacitracin	HPC	0.60	Topical antibiotic
2-Bromo-2-nitropropane-1,3-diol (Bronopol)	PVP	0.25	Cosmetic preservative
Disperse Blue 106	PVP	0.05	Textile dye
None	PVP		(control)
None	HPC		(control)

Review Committee

Table 2 lists the primary reviewers of this supplement and their respective review assignments.

Table 2. Primary reviewers of this supplement.

Specific responsibilities or	Reviewer Name	Document Date

documents used in developing the SBRA		
Regulatory Project Manager	Rana Chattopadhyay	N/A
Regulatory Project Manager	Elizabeth Valenti	
Clinical Review	Ronald L. Rabin, M.D.	10/28/11; 10/31/11
Statistical Review	Lihan Yan, Ph.D.	11/1/11
Product (Testing) Review	Alfred Del-Grosso, Ph.D.	12/13/11
Product Review	Sandra Menzies, M.S.	11/9/11
Product Review	Taruna Khurana, Ph.D.	11/9/11
CMC Review	Daniel Kearns, CSO	11/4/11
Labeling (APLB) Review	Dana Martins, CSO	11/3/11
Biomonitoring Review	Solomon Yimam, CSO	11/7/11

Summary

Mekos submitted the above-cited supplement to their Biologics License Application for their Allergen Patch Test kit (T.R.U.E. TEST). The purpose of the supplement is for the applicant to receive approval to manufacture a new patch test panel, Panel 3, that incorporates the allergens: Gold sodium thiosulfate (GST), Hydrocortisone-17-butyrate (H-17-B), Parthenolide, Methyldibromoglutaronitrile (MDBGN), Bacitracin, 2-Bromo-2-nitropropane-1,3-diol (Bronopol), and Disperse Blue 106. The patch kit also includes a negative control, consisting of an uncoated polyester patch as part of the previously approved Panel 1. With the addition of these seven allergens, the panels have been updated and renumbered as Panels 1.2, 2.2, and 3.2.

Background

Allergic contact dermatitis (ACD) is caused by contact sensitizers that elicit a prototypical delayed-type hypersensitivity reaction (DTH) at the point of contact. The sensitizer is generally a small lipid-soluble molecule that binds to host proteins and thus acts as a hapten, which is presented by host Langerhans cells via MHC II to hapten-specific CD4 T cells. ACD is relatively common in Western populations, and the epicutaneous patch test is generally used to identify the offending substance.

Mekos manufactures and distributes the T.R.U.E. TEST panel of allergen patch tests as a ready-to-use patch test method designed for use by licensed physicians for the diagnosis of allergic contact dermatitis. T.R.U.E. TEST has been evaluated in several large, multi-center clinical studies and is the only combined allergen and patch panel/chamber product currently approved for sale in the United States (U.S.).

As currently licensed, the T.R.U.E. TEST product consists of three panels (pieces of surgical tape [5.2 x 13.0 cm]), each panel containing several polyester patches of approximately 0.81 cm^2. Panel 1.1 contains 11 allergen or allergen mixture patches and one negative control, Panel 2.1 contains 12 allergen patches, and Panel 3.1 contains 5 allergen patches. Each panel is wrapped in its own foil pouch; the pouch containing Panel 2.1 also includes desiccant paper for the purpose of maintaining stability. Each 0.81 cm^2 patch contains the allergen or allergen mix in a dried, uniform gel coating on polyester sheeting. These allergen gel patches are attached to a ----------(b)(4)-------- tape coated with a medical acrylic adhesive. Except for plant-based oils (e.g. poison ivy) and latex, the current set of allergens covers a majority of the known contact allergens in the U.S.

Review of Supplement

On March, 2011, Mekos Laboratories ApS submitted a Clinical Efficacy Supplement to their approved BLA #103738, to include the addition of seven new allergens for use in adults. This change would complete Panel 3.2 by adding six of the seven new allergens, plus the allergen Mercaptobenzothiazole (removed from Panel 2.1). The seventh new allergen, Methyldibromoglutaronitrile, (MDBGN) is added to existing Panel 2.1 (in place of Mercaptobenzothiazole) to make the new Panel 2.2. For consistency, the numbering of Panel 1.1 would be changed to Panel 1.2, although this panel is unchanged. The six allergens selected for inclusion on Panel 3.2 are gold sodium thiosulfate (GST), hydrocortisone-17-butyrate (H-17-B), Parthenolide, bacitracin, 2-Bromo-2-nitropropane-1,3-diol (Bronopol), and Disperse blue 106.

CMC

The name and address of the approved suppliers of the source materials are provided in the following tables.

Table 3. Allergen source materials

[(b)(4)]

Table 4. Non-active Ingredient Source Materials

[(b)(4)]

-----(b)(4)---------
----------(b)(4)----------
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4 pages redacted due to (b)(4)

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

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Analytical Procedures

For each new allergen essentially the same analytical procedures are described for the drug substance and drug product. In each case the analytical method also serves as the identification method for the allergen. The methods of analysis and quality of each assay used is described in the document entitled "Mid-cycle review and information requests," document date 09-Sept-2011. Gold Sodium Thiosulfate is determined as elemental gold by ---------(b)(4)----------. The six other new allergens are determined by methods using ----------(b)(4)----------. Analytical procedural descriptions and validations were generally found satisfactory. A few specific details concerning calculations and assay controls for the gold determination were addressed in an information request on 19-Sept-2011. A satisfactory response to these issues was received on 20-Oct-2011 as part of Amendment 5003.

As originally submitted in the method validations, the linearity of each procedure was evaluated ----------(b)(4)----------. As part of the 19-Sept-2011 IR, a request was made that linearity be evaluated on the basis of reportable results in product matrix. Appendices 13 – 19 of Amendment 5003 reported linearity evaluations based on ----------(b)(4)----------. These were judged to have satisfactorily fulfilled this request.

Drug Substance Specifications (Table 6, below)

Table 6. Accepted specifications for each new drug (allergen) substance.

Allergen Substance	Labeled amount	End of shelf life (b)(4) of labeled amt)
Gold Sodium Thiosulfate	0.075 mg/cm^2	----------(b)(4)------
Hydrocortisone-17-butyrate	0.020 mg/cm^2	----------(b)(4)-------
Bacitracin	0.60 mg/cm^2	----------(b)(4)---
Parthenolide	3.0 ug/cm^2	----------(b)(4)-
Disperse Blue 106	0.050	----------(b)(4)------
2-Bromo-2-nitropropane-1,3-diol	0.25 mg/cm^2	----------(b)(4)---
Methyldibromo-Glutaronitrile	5.0 ug/cm^2	----------(b)(4)-

Three patch materials, gold sodium thiosulfate, bronopol, and bacitracin, were selected for CBER testing based on the analytical procedure used and product type. Assay procedures described by Mekos were replicated at CBER. CBER test results for these three formulated patches for the two lots (Lot numbers C95229 and C95230) submitted in support of this supplement met the specifications proposed by the manufacturer.

Stability results

Table 7 shows the stability specifications and results of testing of three production batches of each drug substance. Stability data were provided for three production batches of T.R.U.E. TEST Panel 2.2, batches ----------(b)(4)----------, and Panel 3.2, batches ------(b)(4)----------.

Three allergens (bacitracin, parthenolide, and MDBGN) did not meet stability criteria at extreme conditions of ----(b)(4)-----. Since the T.R.U.E. TEST is stored at 2-8°C with an expiration date of 24 months, the stability data at extreme conditions are often used in support of shipping temperatures. All new allergens found on production were stable up to 24 months when stored at 5°C. Although some allergens did not meet specifications during high temperature studies, they did meet specifications throughout expiry when stored at the labeled temperature. Therefore the

product must be stored and shipped at the labeled temperature of 2 – 8°C, and should not be exposed to high temperatures for extended periods.

Table 7. Stability specifications and results of testing of each drug substance

Allergen	Specifications (mg/cm^2)	Stability at 5^oC[1] (mg/cm2)	Stability at ----(b)(4)---------- (mg/cm2)	Comments
Gold Sodium Thiosulfate	-----(b)(4)----	-----(b)(4)----	-----(b)(4)----	Met specifications
Hydrocortisone-17-butyrate	-----(b)(4)----	-----(b)(4)----	-----(b)(4)----	Met specifications
Bacitracin	---(b)(4)--	---(b)(4)--	---(b)(4)--	Did not meet specifications at ----(b)(4)--- months when stored at ---(b)(4)-----. However, met specifications through 24 months when stored at correct labeled storage temperatures of 2-8°C.
Parthenolide	-(b)(4)-	-(b)(4)-	-(b)(4)-	Did not meet specifications at ----(b)(4)--- months when stored at ---(b)(4)-----. However, met specifications through 24 months when stored at correct labeled storage temperatures of 2-8°C.
Disperse Blue 106	-----(b)(4)----	-----(b)(4)----	-----(b)(4)----	Met specifications
2-Bromo-2-nitropropane-1,3-diol	---(b)(4)--	---(b)(4)--	---(b)(4)--	Met specifications
Methyldibromo-Glutaronitrile	-(b)(4)-	-(b)(4)-	-(b)(4)-	Did not meet specifications at ----(b)(4)--- months when stored at ---(b)(4)-----. However, met specifications through 24 months when stored at correct labeled storage temperatures of 2-8°C.

[1]Storage time at 5^oC: 3, 6, 9, 12, 18, and 24 months
[2]Storage time at ----------(b)(4)----------

Lot Release

CBER will release T.R.U.E. Test Panels 1.2, 2.2, and 3.2 at the final product stage. All critical product tests will be included in the lot release protocol. Mekos will submit samples and lot release protocols for each lot to CBER for lot release.

Facilities Review

Mekos Laboratories ApS submitted a request for a Categorical Exclusion to omit preparation of an Environmental Assessment, under 21 CFR Part 25.31(b)) as part of the Biologics License Application Supplement 103738/5074. Daniel Kearns, DMPQ/CBER concluded that the request was justified because there is apparently no significant new manufacturing, either from an aspect of quantity (no new facilities, or significant new equipment), or from an aspect of new manufacturing processes (no new purification). Because the product meets the applicable exclusion criteria in 21 CFR Part 25, and there is no information indicating that extraordinary circumstances exist, a pre-approval inspection was not required.

Clinical Data

For each of the seven allergens, there was a first set of Phase 2 studies performed in North America and/or Europe to determine the proper dose of the patches. For these dose-range studies, subjects who were known to be allergic ("known sensitized) to the allergen were defined as those who had a positive reaction to a patch test within the past five years. A positive reaction

to the patch test was defined as ++ (erythema, infiltration, papules, possible discrete papules) or +++ (erythema, infiltration, coalescing vesicles). These subjects were tested with both an ---------(b)(4)---------- test tape, and for reference, a tape including the corresponding allergens in petrolatum or ethanol in concentrations usually used for clinical testing.

Following the dose-ranging studies was a pivotal (Phase 3) trial performed in five centers, four in the U.S., and one in Denmark. The Phase 3 trial is described in detail below.

Dose Ranging Studies

Gold sodium thiosulfate (GST)

The final GST concentration used in this study was selected based on the results from Study Mekos 05 P379/1, a European study that was performed in 2005 in which GST in HPC was tested at concentrations of 0.075, 0.025, 0.0083, 0.0028, and 0.00093 mg/cm^2. Overall, the results of this study indicated that the 0.075 mg/cm^2 dose was optimal (i.e., was the lowest concentration that induced a + or ++ positive reaction in 70% to 90% of gold-sensitized subjects.

Hydrocortisone-17-butyrate (H-17-B)

The final H-17-B concentration was selected based on the results from Study Mekos 09 P335/1, a European study that was performed in 2004 in which H-17-B in PVP was tested at concentrations of 0.15, 0.050, 0.017, 0.0056, and 0.0019, mg/cm^2. Overall, the results of this study indicated that the 0.017 mg/cm^2 dose was optimal (i.e., was the lowest concentration that induced a + or ++ positive reaction 70% to 90% of H-17-B-sensitized subjects). For practical reasons, this concentration was rounded up to 0.020 mg/cm^2.

Methyldibromoglutaronitrile (MDBGN)

The final MDBGN concentration was selected based on the results from Mekos 05 P379/1, a European study that was performed in 2005 in which MDBGN was tested at concentration of 0.015, 0.0050, 0.0017, and 0.00056 mg/cm^2 in HPC, and at 0.015 and 0.0050 mg/cm^2 in PVP. Overall, the results of this study indicated that the 0.005 mg/cm^2 dose in HPC was optimal (i.e. was the lowest concentration that induced a + or ++ positive reaction in 70% to 90% of MDBGN-sensitized subjects). There was no statistical difference between the responses obtained with MDBGN in the two vehicles. Due to the enhanced stability and processing capability of PVP preparations, the final allergen /formulation was 0.005 mg/cm^2 in PVP.

Bacitracin

The final bacitracin concentration used was selected based on the results from Study Mekos 04 P36/2 in the United States in which bacitracin was tested at concentrations of 0.30, 0.15, and 0.075 mg/cm^2 in HPC. Specifically, in this dose-response study, 20 bacitracin-sensitive subjects were patch-tested with a T.R.U.E. TEST panel containing five concentrations of the allergen in HPC, along with a reference standard; 20 subjects reacted to the reference standard. Of these sensitized subjects, 80% (n = 16) had a positive reaction to bacitracin in HPC at a concentration of 0.60 mg/cm^2, which was determined to be the optimal concentration (i. e. was the lowest concentration that induced a + or ++ positive reaction in 70% to 90% of bacitracin-sensitized subjects).

Parthenolide

The final parthenolide concentration was selected based on the results from Study Mekos 05 P379/1, a European study that was performed in 2005 in which parthenolide in PVP was tested at concentrations of 0.10, 0.0033, 0.0011, 0.00037, and 0.00012 mg/cm^2. Overall, the results of this study indicated that the 0.0033 mg/cm^2 dose was optimal (i.e., was the lowest concentration

that induced a + or ++ positive reaction in 70% to 90% of parthenolide-sensitized subjects). For practical reasons, the final dose is 0.003 mg/cm^2.

Disperse Blue 106

The final Disperse Blue 106 concentration was selected based on the results from Study Mekos Mekos 072P3.2 301, a North American study that was performed in 2005. Disperse Blue 106 in PVP was tested at concentrations of 0.17, 0.50, 0.050 mg/cm^2. Overall, the results of this study indicated that the 0.250 mg/cm^2 dose was optimal (i.e., was the lowest concentration that induced a + or ++ positive reaction in 70% to 90% of Disperse Blue 106-sensitized subjects).

Bronopol

The final Bronopol concentration was selected based on the results from Study Mekos Mekos 072P3.2 301, a North American study that was performed in 2005 in which Disperse Blue 106 in PVP was tested at concentrations of 0.125, 0.250, 0.50, and 0.75 mg/cm^2. Overall, the results of this study indicated that the 0.250 mg/cm^2 dose was optimal (i.e., was the lowest concentration that induced a + or ++ positive reaction in 70% to 90% of Bronopol-sensitized subjects)..

Pivotal Trial

The Phase 3 trial "Clinical Evaluation of TRUE TEST Panel 3.2 Allergens: Gold sodium thiosulfate (GST), Hydrocortisone-17-butyrate (H-17-B), Parthenolide, Methyldibromoglutaronitrile (MDBGN), Bacitracin, 2-Bromo-2-nitropropane-1,3-diol (Bronopol), and Disperse blue 106" was conducted at five centers (four in the U.S. and one in Denmark) between 03-June-2008 and 17-August-2009.

The Primary Endpoint of the study was to demonstrate the *diagnostic performance of each of the seven new T.R.U.E. TEST allergens*, including the calculated concordance/discordance between each of the seven new allergens and the corresponding reference allergens in petrolatum or ethanol, and the calculated sensitivity and specificity for each of the seven new T.R.U.E. TEST allergens. Consistent with approval of other T.R.U.E. TEST allergens, there was no threshold of concordance, sensitivity, or specificity that each of the allergen patches must meet—only that those levels be adequately defined in the context of these studies of fifteen sensitive subjects.

The Secondary Endpoint was to demonstrate the *safety of the seven new TRUE TEST allergens including* the frequency and characterization of late and/or persistent reactions, tape-induced irritation at the test site, incomplete panel adhesion, and subject-reported sensations of itching or burning during the test period; a late/persistent reaction was defined as a positive response at Visit 5, and the frequency of AEs and SAEs.

The study population was to include 205 adult subjects who were in general good health, of which at least 100 subjects had suspected contact dermatitis (i.e. "consecutive subjects"), and at least 15 subjects who *for each new* T.R.U.E. TEST allergen, had a positive historical or concurrent reference patch test (15 positive subjects for each of 7 allergens = 105 "sensitive subjects"). A total of 235,(110 consecutive and 125 sensitive) subjects were analyzed.

The study was conducted over 21 days (per subject); On Day 0 (Visit 1) the T.R.U.E. TEST patches were applied to the subjects' upper backs or arms along with the patch test chambers that contained reference allergens corresponding to each T.R.U.E. TEST allergen. The reference allergens were: GST, (b)(4) in petrolatum; H-17-B, (b)(4) in ethanol; MDBGN (with phenoxyethanol, another preservative with which MDBGN is mixed), (b)(4) in petrolatum; Bacitracin, (b)(4) in petrolatum; Parthenolide, (b)(4) in petrolatum; Disperse Blue 106, (b)(4) in

petrolatum; and Bronopol, (b)(4) in petrolatum. These doses were chosen because ----------(b)(4)----------.

On Day 2 (Visit 2), the patches and patch test chambers were removed and all test site skin reactions were evaluated along with any tape irritations. Subject reports of itching and/or burning at the test sites also were recorded during the visit.

Additional evaluations of test site skin reactions were conducted 3 days, 7 days, and 3 weeks (Visits 3, 4, and 5, respectively) after the initial patch application If necessary to verify any of the test site skin reactions, an additional evaluation [Visit 3b] was conducted 4 days after the initial patch application. Adverse events (AEs) and serious adverse events (SAEs) were documented at every study visit, non-negative test sites were photographed at Visits 3, 4, and 5, Late and/or persistent skin reactions were recorded at Visit 5. All subjects exited the study at the completion of Visit 5, which, at the investigator's discretion, may have been over the telephone.

Reactions were assessed as negative (no clinical response), irritant (discrete, patchy, follicular, or homogenous erythema with no infiltration), doubtful (faint macular or homogenous erythema with no infiltration), or positive. Positive reactions were graded as either + (weak positive; erythema, infiltration, discrete papules), ++ (strong positive; erythema, papules, infiltration, descrete vesicles), or +++ (extreme positive; coalescing vesicles, bullous reaction).

Subject Disposition
Of the 235 subjects who enrolled, one did not complete the study because he or she was lost to follow-up. There were no withdrawals due to AE. Of the 125 sensitive subjects who were enrolled, all completed the study.

Protocol Deviations
Few protocol deviations were reported in the study. These deviations, which did not result in exclusion of any subject from either the efficacy or safety analyses, included a minor error in the dating of an informed consent document (resolved through retraining of the investigational center) and 5 out-of-window visits, which were not unexpected given the design of the study. Demographics and Baseline characteristics were extracted from Tables 11-1 and 11-2, and are shown in Tables 8 and 9, respectively.

Table 8. Subject Demographics

Table 11–1: Summary of Subject Demographic Characteristics (All Subjects)

Age (years)	
N	235
Mean	51.8
STD	14.75
Min. to Max.	18 to 85
Sex	
N	235
Male	69 (29.4%)
Female	166 (70.6%)
Race	
N	235
Caucasian	213 (90.6%)
Hispanic	5 (2.1%)
Asian	4 (1.7%)
African American	13 (5.5%)
Other	0 (0.0%)

Table 9. Subject Baseline Characteristics

Table 11–2: Summary of Subject Baseline Characteristics (

Number of subjects	235
Type of dermatitis[a]	
Allergic	212 (90.2%)
Irritant	7 (3.0%)
Atopic	11 (4.7%)
Occupational dermatitis	1 (0.4%)
Other	36 (15.3%)
Current dermatitis symptoms[a]	
Yes	134 (57.0%)
No	101 (43.0%)
Dermatitis symptom areas[b]	
Face and/or scalp and/or neck	28 (20.9%)
Trunk	33 (24.6%)
Arms and/or hands	78 (58.2%)
Legs and/or feet	35 (26.1%)

Efficacy Data (Data on subjects sensitive to the allergens)

Data extracted from Table 11-3 in the BLA show the number of subjects sensitive to each allergen and the magnitude of their previous response to each allergen (Table 10).

Table 10

Table 11–3: Summary of Previous Positive Patch Test Results (Sensitive Subjects)

Number of subjects sensitive to gold sodium thiosulfate	19
Previous positive patch test results to gold sodium thiosulfate[a]	
Weak (nonvesicular) positive reaction (+)	4 (21.1%)
Strong (vesicular) positive reaction (++)	10 (52.6%)
Extreme positive reaction (+++)	5 (26.3%)
Number of Subjects sensitive to hydrocortisone-17-butyrate	20
Previous positive patch test results to hydrocortisone-17-butyrate[a]	
Weak (nonvesicular) positive reaction (+)	7 (35.0%)
Strong (vesicular) positive reaction (++)	9 (45.0%)
Extreme positive reaction (+++)	4 (20.0%)
Number of subjects sensitive to methyldibromoglutaronitrile	29
Previous positive patch test results to methyldibromoglutaronitrile[a]	
Weak (nonvesicular) positive reaction (+)	17 (58.6%)
Strong (vesicular) positive reaction (++)	11 (37.9%)
Extreme positive reaction (+++)	1 (3.4%)
Number of subjects sensitive to bacitracin	24
Previous positive patch test results to bacitracin[a]	
Weak (nonvesicular) positive reaction (+)	7 (29.2%)
Strong (vesicular) positive reaction (++)	10 (41.7%)
Extreme positive reaction (+++)	7 (29.2%)
Number of subjects sensitive to parthenolide	18
Previous positive patch test results to parthenolide[a]	
Weak (nonvesicular) positive reaction (+)	4 (22.2%)
Strong (vesicular) positive reaction (++)	10 (55.6%)
Extreme positive reaction (+++)	4 (22.2%)
Number of subjects sensitive to disperse blue 106	17
Previous positive patch test results to disperse blue 106[a]	
Weak (nonvesicular) positive reaction (+)	9 (52.9%)
Strong (vesicular) positive reaction (++)	6 (35.3%)
Extreme positive reaction (+++)	2 (11.8%)
Number of subjects sensitive to bronopol	23
Previous positive patch test results to bronopol[a]	
Weak (nonvesicular) positive reaction (+)	16 (69.6%)
Strong (vesicular) positive reaction (++)	6 (26.1%)
Extreme positive reaction (+++)	1 (4.3%)

Data extracted from Tables 11-4 and 11-5 show the reactions of these subjects to patch testing for this trial as observed during Visit 3 (48 hours) and Visit 4 (72 hours), respectively (Tables 11 and 12).

Table 11. Frequency of Reactions at Visit 3.

Table 11–4: Frequency of Positive, Negative, Irritant, and Doubtful Reactions at Visit 3 (Sensitive Subjects)

	Gold Sodium Thiosulfate (N=19)	Hydrocortisone-17-Butyrate (N=20)	Methyldibromo-glutaronitrile (N=29)	Bacitracin (N=24)
Positive Reaction (+, ++, +++)	15 (78.9%)	12 (60.0%)	4 (13.8%)	15 (62.5%)
95% confidence interval[a]	(54.4%, 93.9%)	(36.1%, 80.9%)	(3.9%, 31.7%)	(40.6%, 81.2%)
Negative Reaction	2 (10.5%)	5 (25.0%)	23 (79.3%)	8 (33.3%)
95% confidence interval[a]	(1.3%, 33.1%)	(8.7%, 49.1%)	(60.3%, 92.0%)	(15.6%, 55.3%)
Irritant Reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
95% confidence interval[a]	(0.0%, 17.6%)	(0.0%, 16.8%)	(0.0%, 11.9%)	(0.0%, 14.2%)
Doubtful Reaction	2 (10.5%)	3 (15.0%)	2 (6.9%)	1 (4.2%)
95% confidence interval[a]	(1.3%, 33.1%)	(3.2%, 37.9%)	(0.8%, 22.8%)	(0.1%, 21.1%)

	Parthenolide (N=18)	Disperse Blue 106 (N=17)	Bronopol (N=23)
Positive Reaction (+, ++, +++)	13 (72.2%)	9 (52.9%)	7 (30.4%)
95% confidence interval[a]	(46.5%, 90.3%)	(27.8%, 77.0%)	(13.2%, 52.9%)
Negative Reaction	4 (22.2%)	8 (47.1%)	14 (60.9%)
95% confidence interval[a]	(6.4%, 47.6%)	(23.0%, 72.2%)	(38.5%, 80.3%)
Irritant Reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)
95% confidence interval[a]	(0.0%, 18.5%)	(0.0%, 19.5%)	(0.0%, 14.8%)
Doubtful Reaction	1 (5.6%)	0 (0.0%)	2 (8.7%)
95% confidence interval[a]	(0.1%, 27.3%)	(0.0%, 19.5%)	(1.1%, 28.0%)

Source: Table 14.2.3.2.1, Table 14.2.3.2.2, Table 14.2.3.2.3, Table 14.2.3.2.4, Table 14.2.3.2.5, Table 14.2.3.2.6, and Table 14.2.3.2.7

[a] 95% confidence intervals calculated using SAS PROC FREQ with the exact binomial option.

Note: The reactions to each allergen are presented only for subjects sensitive to that specific allergen (e.g., reactions to gold sodium thiosulfate among subjects with sensitivity to gold sodium thiosulfate).

Table 12. Frequency of Reactions at Visit 4.

Table 11–5: Frequency of Positive, Negative, Irritant, and Doubtful Reactions at Visit 4 (Sensitive Subjects)

	Gold Sodium Thiosulfate (N=19)	Hydrocortisone-17-Butyrate (N=20)	Methyldibromo-glutaronitrile (N=29)	Bacitracin (N=24)
Positive Reaction (+, ++, +++)	15 (78.9%)	11 (55.0%)	3 (10.3%)	14 (58.3%)
95% confidence interval[a]	(54.4%, 93.9%)	(31.5%, 76.9%)	(2.2%, 27.4%)	(36.6%, 77.9%)
Negative Reaction	3 (15.8%)	7 (35.0%)	26 (89.7%)	8 (33.3%)
95% confidence interval[a]	(3.4%, 39.6%)	(15.4%, 59.2%)	(72.6%, 97.8%)	(15.6%, 55.3%)
Irritant Reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
95% confidence interval[a]	(0.0%, 17.6%)	(0.0%, 16.8%)	(0.0%, 11.9%)	(0.0%, 14.2%)
Doubtful Reaction	1 (5.3%)	2 (10.0%)	0 (0.0%)	2 (8.3%)
95% confidence interval[a]	(0.1%, 26.0%)	(1.2%, 31.7%)	(0.0%, 11.9%)	(1.0%, 27.0%)

	Parthenolide (N=18)	Disperse Blue 106 (N=17)	Bronopol (N=23)
Positive Reaction (+, ++, +++)	12 (66.7%)	9 (52.9%)	5 (21.7%)
95% confidence interval[a]	(41.0%, 86.7%)	(27.8%, 77.0%)	(7.5%, 43.7%)
Negative Reaction	5 (27.8%)	8 (47.1%)	15 (65.2%)
95% confidence interval[a]	(9.7%, 53.5%)	(23.0%, 72.2%)	(42.7%, 83.6%)
Irritant Reaction	0 (0.0%)	0 (0.0%)	2 (8.7%)
95% confidence interval[a]	(0.0%, 18.5%)	(0.0%, 19.5%)	(1.1%, 28.0%)
Doubtful Reaction	1 (5.6%)	0 (0.0%)	1 (4.3%)
95% confidence interval[a]	(0.1%, 27.3%)	(0.0%, 19.5%)	(0.1%, 21.9%)

The concordance between T.R.U.E. TEST and reference allergen reactivity (in a chamber with either petrolatum or ethanol) is shown in data extracted from Table 11-6 (Table 13).

Table 13. Concordance between T.R.U.E. TEST and Reference Allergens.

	Percent Agreement[a]		Kappa Statistic[b]	
GST 0.075 mg/cm^2	Estimate	84.2%	Estimate	0.627
	95% CI[c]	(60.4%, 96.6%)	95% CI	(0.268, 0.986)
			P-value	0.003
H-17-B 0.020 mg/cm^2	Estimate	90.0%	Estimate	0.780
	95% CI[c]	(68.3%, 98.8%)	95% CI	(0.492, 1.000)
			P-value	<0.001
MDBGN 0.0055 mg/cm^2	Estimate	62.1%	Estimate	0.224
	95% CI[c]	(42.3%, 79.3%)	95% CI	(-0.054, 0.501)
			P-value	0.119
Bacitracin 0.60 mg/cm^2	Estimate	75.0%	Estimate	0.455
	95% CI[c]	(53.3%, 90.2%)	95% CI	(0.106, 0.803)
			P-value	0.017
Parthenolide 0.0030 mg/cm^2	Estimate	94.4%	Estimate	0.852
	95% CI[c]	(72.7%, 99.9%)	95% CI	(0.575, 1.000)
			P-value	<0.001
Disperse blue 106 0.050 mg/cm^2	Estimate	88.2%	Estimate	0.764
	95% CI[c]	(63.6%, 98.5%)	95% CI	(0.457, 1.000)
			P-value	0.002
Bronopol 0.25 mg/cm^2	Estimate	82.6%	Estimate	0.566
	95% CI[c]	(61.2%, 95.0%)	95% CI	(0.218, 0.914)
			P-value	0.003

Source: Table 14.2.3.1.1, Table 14.2.3.1.2, Table 14.2.3.1.3, Table 14.2.3.1.4, Table 14.2.3.1.5, Table 14.2.3.1.6, and Table 14.2.3.1.7

[a] Percent agreement = [observed agreement / total] x 100.

[b] Kappa statistic = $[(p_{\text{observed agreement}} - p_{\text{expected agreement}}) / (1 - p_{\text{expected agreement}})] \times 100$. P-value is from a 2-sided asymptotic test against kappa equal to 0.

[c] 95% confidence interval (CI) calculated using SAS PROC FREQ with the exact binomial option.

Note: The concordance data for each allergen are presented only for subjects sensitive to that specific allergen (e.g., concordance between T.R.U.E. TEST gold sodium thiosulfate and reference gold sodium thiosulfate results among subjects with sensitivity to gold sodium thiosulfate).

Data showing concordance between the T.R.U.E. TEST allergens and historical patch testing among sensitive subjects are shown in data extracted from Table 11-7 (Table 14).

Allergen	Percent agreement Estimate (95% CI)
Gold Sodium Thiosulfate	78.9% (54.4%, 93.9%)
Hydrocortisone-17-butyrate	65.0% (40.8%, 84.6%)
Bacitracin	75.0% (53.3%, 90.2%)
Parthenolide	72.2% (46.5%, 90.3%)
Disperse Blue 106	52.9% (27.8%, 77.0%)
2-Bromo-2-nitropropane-1,3-diol	34.8% (16.4%, 57.3%)
Methyldibromo-Glutaronitrile	17.2% (5.8%, 35.8%)

Sensitivity and specificity

As shown in Table 15, the sensitivity of each of the new allergens, as defined by a positive reaction to the T.R.U.E. TEST allergen by a subject who has a positive reaction to the reference allergen, was at least 88.9% for six of the contact allergen studies. The sensitivity, however, to

MDBGN was 28.6%. Subjects who were considered positive to MDBGN may actually be allergic to phenoxyethanol, a compound with which MDBGN is combined. Sensitivity and specificity extracted from Table 11-9 are shown below in Table 15.

Table 15. Sensitivity and Specificity of T.R.U.E. Test Allergens in Sensitive Subjects

Table 11–9: Sensitivity and Specificity of T.R.U.E Test Allergens (Sensitive Subjects)

	Sensitivity[a]	Specificity[b]
GST 0.075 mg/cm^2	100.0%	57.1%
95% confidence interval[c]	(73.5%, 100.0%)	(18.4%, 90.1%)
H-17-B 0.020 mg/cm^2	92.3%	85.7%
95% confidence interval[c]	(64.0%, 99.8%)	(42.1%, 99.6%)
MDBGN 0.0055 mg/cm^2	28.6%	93.3%
95% confidence interval[c]	(8.4%, 58.1%)	(68.1%, 99.8%)
Bacitracin 0.60 mg/cm^2	92.9%	50.0%
95% confidence interval[c]	(66.1%, 99.8%)	(18.7%, 81.3%)
Parthenolide 0.0030 mg/cm^2	92.9%	100.0%
95% confidence interval[c]	(66.1%, 99.8%)	(39.8%, 100.0%)
Disperse blue 106 0.050 mg/cm^2	88.9%	87.5%
95% confidence interval[c]	(51.8%, 99.7%)	(47.3%, 99.7%)
Bronopol 0.25 mg/cm^2	100.0%	78.9%
95% confidence interval[c]	(39.8%, 100.0%)	(54.4%, 93.9%)

Taken together, these data demonstrate acceptable sensitivity of six of these seven T.R.U.E. TEST allergen tests. Because the values for specificity are less than ideal, these tests are of value, not as a definitive test, but as an aid for the diagnosis of sensitivity to the allergens.

Safety

Of the 235 subjects enrolled in the study, ten subjects reported 11 AEs, all of which were not serious and mild (eight AEs) or moderate (three AEs) in severity. None of the moderate AEs were related to the study drug(s). There were four episodes of intense itching or pruritus, and one flare of pre-existing hand eczema during the first three days of testing that were possibly or probably related to the patch testing.

The T.R.U.E. TEST panel adhered well to skin, although about 50% of subjects experienced skin irritation. Most of the subjects who experienced itching and burning in response to the panels were allergic to at least one of the allergens in the panel.

Seven of the 110 consecutive subjects had late skin reactions. Six of these were to GST, one to MDBGN, and one to Disperse Blue 106).

Among the 110 consecutive subjects, the most frequently observed persistent skin reactions occurred among GST-sensitive subjects. Seven reports each of erythema and infiltration, four reports of pruritis, and one report of hyperpigmentation. Among parthenolide-sensitive subjects, there were six reports each of infiltration and hyperpigmentation each, five reports of pruritis, four reports of erythema, and one report of hypopigmentation.

Among the sensitive subjects, ten experienced persistent reactions to one or two of the allergens the T.R.U.E. TEST panel. No one allergen was more associated with these persistent reactions.

Statistical Review

The statistical review is primarily based on the Phase III efficacy study (Study 301) which was conducted to support the proposed label indications. This study enrolled 125 sensitive subjects to at least one of 7 new allergens included in the patch and 100 additional consecutive subjects. The primary objective of the study was to evaluate the diagnostic performance of the product.

- The sample size consideration was not based on the primary objective of evaluating the diagnosis performance of the new allergens. Instead, it was based on the hypothesis that the adverse event rates were no more than what were observed historically. In the protocol, there appear to be inconsistencies in the hypothesis setup and statistical power calculations.

- Because of the small sample size of the sensitive subject in each type of allergens (N=17-29), large confidence intervals were observed for the concordance measures in terms of percent agreement, sensitivity and specificity. For example, when comparing to the reference allergens, the sensitivities of the T.R.U.E patch ranged from 29% to 100% with 95% CIs ranging 8% to 73%. It appears that the MDBGN allergen performed relatively poorly.

  Since there were no pre-specified criteria for the success of the study, the statistical reviewer was unable to evaluate the observed data against expectations. The reviewer deferred to the committee with regard to CBER acceptance criteria for granting the license for the product.

The committee acknowledges the statistical weakness of the clinical trials. Data derived from these trials, however, can still be used in support of effectiveness for the following reasons: While the contact hypersensitivity to any one of these allergens is common, sensitivity to each of these allergens (other than nickel and perhaps a few others), is not very common. Therefore, it is not feasible to design studies with a sample size that could adequately test a threshold of sensitivity for each of these allergens. Furthermore, since most of these allergens are relatively easy to avoid, those who have previously been diagnosed with contact hypersensitivity to one of these allergens will avoid the offending substance. If avoidance is long enough, subjects may need repeated "real-world" exposures to elicit a positive reaction. However, such loss of clinical evidence of sensitivity further limits study size, and accounts for the wide CI observed in this study.

Labeling and Prescribing Information Package Insert

The Package Insert (PI) required complete revision in order to conform to PLR format. Review (November 3, 2011) by Dana C. Martin, CSO, identified multiple deficiencies that required further revision by the applicant. Internal meetings for the purpose of review and revision of the Package Insert took place on the following dates in 2011: September 28, October 12, October 17, November 3, December 8, 16, 21, and 27.

During the conference on December 21, 2011, it was discussed that five of the eleven studies of allergens included subjects less than 18 years, and data derived from these studies were included in the Package Insert. Because the product will be approved only for use in adults, however, inclusion of these data in the PI were in clear violation of 21 CFR 201.57(c)(2)(i)(F)(v) and 21 CFR 201.57(c)(15)(i) because inclusion of pediatric data in the PI may imply or suggest that the allergen test panels are indicated for that age group, when in fact, the product will be approved

for adults. Therefore, on December 23, 2011, the sponsors were instructed to revise the PI during a teleconference and via email. The package insert also required additional revisions that were discussed during that teleconference or by additional emails. The requested revisions were received by the agency on January 9, 2012.

In the interim, the CBER reviewers consulted dermatologists in DDDP, CDER to insure that clinical terminology in the PI is correct, accurate, and consistent with that used by practicing dermatologists. CBER received the consultation memorandum from Patricia C. Brown, MD, Dermatology Medical Officer, DDDP, on January 3, 2012. After review of the revisions submitted by the sponsor, and review of the dermatology consult, an internal meeting took place on January 10, 2012.

The agency requested additional revisions, some of which were minor edits, and some of which were those suggested by the dermatology consultant. After additional edits, the final version of the package insert was approved on February 13, 2012.

Advisory Committee Meeting

During internal discussions, the committee agreed that it is not necessary to seek the opinion of the Allergen Product Advisory Committee (APAC) to approve this BLA supplement. Dr. Norman Baylor, then Director of OVRR, and Dr. Marion Gruber, current Director (Acting) of OVRR, concurred with committee position.

PREA Studies

In compliance with the Pediatric Research Equity Act, the sponsor has studied the original 28 allergen panel set in pediatric subjects in Study Mekos 07 29P1/2/3 401. A study of the seven new allergens, Mekos 10 7P3.2 401, is ongoing. The sponsor is expected to seek approval of the product for children and adolescents 6-17 years of age in the near future. The FDA PREA committee agreed with the sponsor that the product is not relevant to children less than six years of age, and thus, it will neither be tested nor approved in children less than six years of age.

Reviewer Conclusions

The T.R.U.E. TEST panel is the only product licensed in the U.S. for testing patients for the presence of contact dermatitis. The seven new allergens that will be added to existing Panels 2.1 and 3.1 are clinically significant, and the applicant has demonstrated that the T.R.U.E. TEST panels are acceptably specific and sensitive. The T.R.U.E. TEST Panels 1.2, 2.2, and 3.2 are safe for use in adults 18 years of age and older.

For reasons summarized in section “Statistical review”, the design of the Phase 3 study (as well as the previous studies designed for approval of other T.R.U.E. TEST allergens) did not include a threshold of concordance, sensitivity, or specificity that each of the allergen patches must meet—only that those levels be adequately defined in the context of these studies of fifteen sensitive subjects.

The applicants, Mekos Laboratories AS (and their U.S. representatives), were informed that the small study size may result in wide CIs of the efficacy data. These efficacy data will be included in the Package Insert so that clinicians may be properly informed of the demonstrated efficacy of this diagnostic product.

In summary the committee recommends approval of the seven additional allergens included in the updated panels to aid in the diagnosis of allergic contact dermatitis or sensitization of an adult who is 18 years of age and above, and is suspected to be allergic to at least one of the allergens in the panel.

This sBLA should not be approved as requested by the applicant for the evaluation of ----------*(b)(4)*----------. No original data were submitted to support these indications.