

Summary Basis for Regulatory Action Template

Date: October 17, 2014

From: Taruna Khurana, PhD, Review Committee Chair

BLA/STN: 103738/5118

Applicant Name: SmartPractice (U.S. license 1623)

Date of Submission: December 19, 2013

Review Goal Date: October 19, 2014

Proprietary Name: T.R.U.E. TEST

Established Name: Multiple Products: Allergen Patch Test Kit

Reason for the Submission: To include a change in the excipient and dose strength for neomycin sulfate, potassium dichromate and fragrance mix, as well as the change in the declared labeled dose for thiuram mix.

Recommended Action: Approval

Signatory Authorities Action:

Office Signatory Authority: Jay E. Slater, M.D.
Director, Division of Bacterial, Parasitic and Allergenic Products
Office of Vaccines Research and Review

- I concur with the summary review.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

Specific documentation used in developing the SBRA	Reviewer Name	Document Date
Clinical Review	Ronald L. Rabin, M.D.	9/15/ 2014
Statistical Review	Tielin Qin, Ph.D.	8/28/ 2014
CMC Review	Taruna Khurana, Ph.D.	9/22/ 2014
Methods Validation Review	Alfred Del-Grosso, Ph.D.	9/25/ 2014
Bioresearch Monitoring Review	Lillian Ortega, M.PH	7/30/ 2104
Advertising and Promotional Labeling	Kristine T. Khuc, Pharm.D.	6/05/2014

1. Introduction

T.R.U.E. TEST (Multiple Products: Allergen Patch Test Allergen Patch Test Kit) is currently licensed in the U.S. as an epicutaneous patch test for use as an aid in the diagnosis of allergic contact dermatitis in persons 18 years of age and older whose history suggests sensitivity to one or more of the 35 substances included in patches on the T.R.U.E. TEST panels.

The test kit contains three multi-patch panels, numbered as Panels 1.2, 2.2 and 3.2. Panel 1.2 contains 11 allergen patches and a negative control, Panel 2.2 contains 12 allergen patches, and Panel 3.2 contains 12 allergen patches. Each patch contains a specific allergen in a uniform gel coating on a patch of polyester sheeting.

In this supplement the Applicant proposes to change the formulation of three allergen patches contained in Panel 1.2, and provides chemistry, manufacturing and controls (CMC) data and clinical bioequivalence data to support these changes. The Applicant proposes to change the Package Insert and the carton and container (foil) labels to reflect these changes. The Applicant also proposes to update the labeling to accurately declare the dose of a fourth allergen patch (thiuram mix), based on a statistical analysis of product quality data. These provided changes are as follows:

In panel 1.2:

For the neomycin sulfate patch (position 3), the excipient, methylcellulose, will be changed to polyvinylpyrrolidone (PVP), and the labeled amount of neomycin will be changed from 0.23 mg/cm² to 0.60 mg/cm².

For the potassium dichromate patch (position 4), the excipient hydroxypropyl (HPC) will be changed to PVP, and the labeled amount of potassium dichromate will be changed from 0.023 mg/cm² to 0.054 mg/cm².

For the Fragrance mix patch (position 6), the excipient, HPC with β -cyclodextrin, will be changed to PVP with β -cyclodextrin, and the labeled amount of Fragrance mix will be changed from 0.043 mg/cm² to 0.050 mg/cm².

In Panel 2.2:

For the thiuram mix patch (position 24), the declared labeled dose of thiuram mix will be changed from 0.025 mg/cm² to 0.027 mg/cm².

All three panels (1.2, 2.2 and 2.3) will be renumbered as Panels 1.3, 2.3, and 3.3, respectively.

2. Background

Allergic contact dermatitis (ACD) is caused by a contact allergen that elicits a prototypical delayed-type hypersensitivity reaction at the point of contact. The contact allergen is generally a low molecular weight 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 T lymphocytes. The epicutaneous patch test is used as an aid in the diagnosis of ACD.

Regulatory History

When originally licensed in July 1990, the T.R.U.E. TEST (Thin Layer Rapid Use Epicutaneous Test) contained 23 allergen patches divided across two panels. In 2007 two supplements (STN 103738/5019 and STN 103738/5027) were approved to include a total of five new allergens on a new panel (3.1). In 2012 a supplement (STN 103738/5074) was approved to include seven additional allergen patches, resulting in a total number of 35 allergen patches divided across three panels, numbered 1.2, 2.2 and 3.2, respectively.

Formulation changes to an approved patch test kit, such as the T.R.U.E. TEST, may require supportive clinical data that demonstrate bioequivalence of the new formulation to the old formulation. The supplement approved in 2012 (STN 103738/5074) included changes to the thimerosal patch. Study SPD 07 2P1/2 401, a single study to evaluate the bioequivalence of a reformulation of two different allergen patches (i.e., thimerosal and fragrance mix) to each respective original patch, was included in that supplement to support the changes to the thimerosal patch. The Applicant provides study SPD 07 2P1/2 401 in the present supplement to support changes to the fragrance mix patch which is contained in Panel 2.1 of the T.R.U.E. TEST.

3. Chemistry Manufacturing and Controls (CMC)

a) Product quality

Table 1 below summarizes the formulation changes made to the specific allergen patches in the T.R.U.E. TEST that were evaluated in clinical bioequivalence studies in support of this supplement.

Table 1. Summary of Proposed Changes in Labeled Patch Concentrations and Vehicles

Allergen	Current labeled dose (mg/cm ²)	Current Patch Vehicle	Proposed labeled dose (mg/cm ²)	Proposed patch vehicle
Potassium dichromate	0.023	Hydroxypropyl cellulose	0.054	Polyvinylpyrrolidone
Neomycin sulfate	0.23	Methylcellulose	0.60	Polyvinylpyrrolidone
Fragrance mix	0.43	β -cyclodextrin and Hydroxypropylcellulose	0.50	β -cyclodextrin and Polyvinylpyrrolidone
Thiuram mix	0.025	Polyvinylpyrrolidone	0.027	Polyvinylpyrrolidone

CMC data to support the noted formulation changes for each of the four allergen patches listed in Table 1 above are summarized below.

Potassium dichromate patch (Position 4, Panel 1.2)

Basis for formulation and label changes

Manufacture of the potassium dichromate patch involves application of a gel containing a mixture of the vehicle and allergen to polyester sheeting. The Applicant proposes to change the vehicle from hydroxypropyl cellulose (HPC) to polyvinylpyrrolidone (PVP) based on experience with manufacturing difficulties presented by the current vehicle. In addition, the Applicant proposes to increase the dose of potassium chromate in T.R.U.E. TEST from 0.023 mg/cm² to 0.054 mg/cm² to avoid false negative reactions.

Manufacturing overview

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

Stability studies

Stability studies of the reformulated potassium dichromate patch were performed at both 5°C and under accelerated conditions of ----- (b)(4) ----- for 24 months. Stability data from these studies support the currently approved expiration date of 2 years from the date of manufacture when stored at 2-8°C.

Identity and potency test methods and validation

----- (b)(4) ----- is used as the ----- (b)(4) -----

----- . The method was validated for specificity, linearity, accuracy, precision and robustness.

Neomycin sulfate patch (Position 3, Panel 1.2)

Basis for formulation and label changes

Manufacture of the neomycin sulfate patch involves application of a gel containing a mixture of the vehicle and allergen to polyester sheeting. The Applicant proposes to increase the neomycin sulfate concentration from 0.23 mg/cm² to 0.60 mg/cm² in the neomycin patch to improve the positivity frequency of the patch. The Applicant reports that in order to increase the concentration of neomycin sulfate a change in the vehicle is necessary and therefore, proposes to change the vehicle from methylcellulose to PVP to allow suitable formulation of the higher allergen content level.

Manufacturing overview

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

Stability studies

Stability studies of the reformulated neomycin patch were performed at both 5°C and under accelerated conditions of -----(b)(4)---- for 24 months. Stability data from these studies support the currently approved expiration date of 2 years from the date of manufacture when stored at 2-8°C. Additionally the Applicant is performing an ongoing stability study on (b)(4) production batches stored for 24 months at 5°C and at accelerated conditions ----(b)(4)---- and will submit the results to the Agency when available.

Identity and potency test methods and validation

----- (b)(4) ----- is used as the identity test for neomycin sulfate patches. The (b)(4) method was validated for specificity.

The potency of the neomycin sulfate patch is determined by -----(b)(4)----- . This method is used for both stability and product release testing. This method is validated for specificity, linearity, accuracy, precision and robustness.

Fragrance Mix Patch (Position 6 Panel 1.2)

Basis for formulation and label changes

Manufacture of the fragrance mix patch involves application of a gel containing a mixture of the vehicle and allergen to polyester sheeting. The Applicant proposes to improve the patch by increasing the concentration of fragrance mix from 0.43 mg/cm² to 0.50 mg/cm² and by changing the vehicle from HPC/β-cyclodextrin to PVP/β-cyclodextrin, because PVP has a stabilizing effect on the gel and ensures an even application of the gel to the polyester sheeting.

Manufacturing overview

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

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

5. Clinical Pharmacology

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

6. Clinical/Statistical

a) Clinical program

This supplement contains data from two clinical bioequivalence studies, SPD 07 2P1/2 401 and SPD 09 P1401, to support the changes in formulation for three of the 11 allergen patches currently in Panel 1.2 of T.R.U.E. TEST and changes in the labeling. These clinical studies are summarized below.

Study SPD 09 P1401

This open label, prospective, single-center study evaluated the bioequivalence of the neomycin sulfate (neomycin) in PVP formulation to the neomycin in MC formulation and the potassium dichromate in PVP formulation to the potassium dichromate in HPC formulation. Assessment of bioequivalence was based on concordance between subjects' reactions to the new and current formulations of each allergen patch. The study population included 40 subjects (20 neomycin sensitive and 20 potassium dichromate sensitive), 18 years of age or older, with clinical histories of contact dermatitis and positive patch test results (current or within the prior ten years) to the existing T.R.U.E. TEST allergens. The investigational allergen patches were applied at Visit 1 on Day 0. At Visit 2 on Day 2 the patches were removed and skin reactions and adverse events (AEs) were recorded. Subjects returned for Visit 3 on Day 3, Visit 4 on Day 7, and Visit 5 on Day 21 for assessment. Skin reactions to the panels were graded as extreme positive, strong positive, weak positive, irritant and doubtful using a photograph guide.

For the evaluation of bioequivalence, a positive reaction was defined as a positive response at Visit 3, and/or Visit 4, and/or Visit 5. For both allergen patches, concordance and discordance (with 95% confidence intervals [CIs]) between the current and new formulations were calculated. In addition, the overall percent agreement and Cohen's kappa statistic were calculated between test results for the current and new formulations. A significant kappa value indicated that the observed agreement between the two formulations for each allergen patch exceeded random chance.

Primary Efficacy Results

Table 2 shows the level of concordance between neomycin (0.23 mg/cm²) in the current MC vehicle and neomycin (0.60 mg/cm²) in the PVP vehicle. Table 3 shows the level of concordance between potassium dichromate (0.23 mg/cm²) in the current HPC vehicle and potassium dichromate (0.054 mg/cm²) in the PVP vehicle.

Table 2: Concordance/discordance for Neomycin Sulfate Formulations

	MC Positive	MC negative	Total
PVP Positive	13	1	14
PVP Negative	3	3	6
Total	16	4	20
Percent agreement ^a			
Estimate	16/20 (80%)		
95% Confidence Interval	56.3%, 94.3%		
Kappa statistic			
Estimate	0.47		
P-value	0.028		

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

Table 3: Concordance/discordance for Potassium Dichromate Formulations

	HPC Positive	HPC Negative	Total
PVP Positive	16	1	17
PVP Negative	0	3	3
Total	16	4	20
Percent agreement ^a			
Estimate	19/20 (95%)		
95% Confidence Interval	75.1%, 99.9%		
Kappa statistic			
Estimate	0.828		
P-value	< 0.001		

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

Summary of Clinical Bioequivalence

The results of this study demonstrated 80% concordance between the 0.23 mg/cm² neomycin MC patch formulation and 0.60 mg/cm² neomycin PVP patch formulation and 95% concordance between the 0.023 mg/cm² potassium dichromate HPC patch formulation and the 0.054 mg/cm² potassium dichromate PVP patch formulation based on subjects' reactions to each patch.

Study SPD 07 2P1/2 401

This open label, prospective, multi-center study evaluated the bioequivalence of the reformulated fragrance mix patch to the current fragrance mix patch. The study population included 50 subjects, 18 years of age or older, 27 subjects were fragrance sensitive and 23 were thimerosal sensitive. The test allergens were housed on a T.R.U.E. TEST patch that included the following panels as a test product (Batch 07011):

- Fragrance mix, 0.50* mg/cm² with β-cyclodextrin in PVP
- Fragrance mix, 0.43 mg/cm² with β-cyclodextrin in HPC
- Thimerosal, -----(b)(4)-----
- Thimerosal, -----(b)(4)-----
- PVP (negative control)
- HPC (negative control)
- PVP with β-cyclodextrin (negative control)

- HPC with β -cyclodextrin (negative control)

*[Note: The concentration of the fragrance mix in PVP patch was erroneously reported as 0.43 mg/cm² (page 30 of 283, Table 9.4.2-1) in the final study report provided in the supplement. During the review of this supplement, the Applicant provided amendments to the final study report with a corrected concentration of 0.50 mg/cm² with β -cyclodextrin in PVP.]

Subjects also had commercially available reference allergens in petrolatum applied to their backs within patch test chambers as reference products. These reference allergens included fragrance mix, (b)(4), and thimerosal, (b)(4). Bioequivalence was determined in 50 adult "sensitive" subjects who had a clinical history of contact dermatitis and a positive patch test (current or within the prior five years) to the corresponding reference allergen in petrolatum (fragrance mix and/or thimerosal). Skin reactions to the panels were graded in the same manner as in Study SPD 09 P1401. Concordance between the two formulations of the fragrance mix patch in Panel 1.2 of the T.R.U.E. TEST patch (HPC versus PVP vehicles) was evaluated. Concordance between each patch and the "gold standard" of the respective allergen in a petrolatum chamber was also evaluated.

As presented in Table 4, the study did not demonstrate concordance between fragrance mix in the current HPC vehicle and fragrance mix in the PVP vehicle. However, these data suggest that there was a better response to the fragrance mix PVP formulation than the fragrance mix HPC formulation

Table 4: Concordance/discordance for fragrance mix patch formulations

	HPC Negative	HPC positive	Total
PVP Negative	13	5	18
PVP Positive	5	4	9
Total	18	9	27
Percent agreement ^a			
Estimate	17/27 (63.0%)		
95% Confidence Interval	42.4%, 80.6%		
Kappa statistic			
Estimate	0.167 (-0.217, 0.551)		
P-value	0.386		

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

The study demonstrated that compared to the reference of fragrance mix in a petrolatum chamber, more subjects who were considered sensitive to the fragrance mix reacted to the PVP preparation than the current HPC preparation. In addition, fewer subjects who were considered not sensitive to fragrance mix reacted to the PVP preparation than the current HPC preparation. Therefore, the PVP preparation may be an improvement in the clinical utility of the T.R.U.E. TEST patch to diagnose and to rule out allergic sensitivity to fragrances.

A statistical issue that arose during the review of this supplement concerned how sensitivity and specificity were reported in the bioequivalence studies. However, for the purpose of supporting the specific formulation changes, and in particular in the context of the comparison with the fragrance mix in the petrolatum chamber, the clinical bioequivalence data as provided in the supplement are adequate.

b) Bioresearch Monitoring Review

The clinical site of study SPD 09 P1401 (Odense University Hospital, Denmark) was inspected under the Agency's Bioresearch Monitoring program. The inspection report for this site was received and reviewed, and did not reveal any problems that impacted the data submitted in this efficacy supplement.

c) Pediatric Research Equity Act (PREA)

This efficacy supplement is not subject to the requirements of PREA, as the studies were not designed to support approval of a formulation with a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

7. Safety

Overview

Safety of the reformulated neomycin sulfate, potassium dichromate and fragrance mix patches was assessed in the two clinical bioequivalence studies as summarized below. No safety signals or trends were observed following exposure to any of the test or control panels.

Study SPD 09 P1401

This study compared the safety of the reformulated potassium dichromate and neomycin sulfate patches to the existing patches for each allergen by assessing irritation and extreme responses. Two of the 20 neomycin sensitive subjects experienced AEs. One subject reported persistent local itching on the day of application. The other subject reported a flare-up of eczema of the hands and dryness of the skin, as well as acid reflux, 3-7 days after test application. None of the potassium dichromate sensitive subjects experienced AEs. No late reactions were observed but there were persistent reactions reported for both formulations of each allergen at 19-23 days after test application. There were no deaths.

Study SPD 07 2P1/2 401

This study compared the safety of the reformulated fragrance mix patch to the existing patch by assessing irritation and extreme responses. A single serious and severe AE was reported (right femoral sheath placed secondary to transient ischemic attack/carotid stenosis) at 19-23 days after test application. This was considered to be unrelated to the study drug. A bladder infection reported by one subject at seven days after test application was considered to be unrelated. Related, non-serious AEs included three reports of mild itching and one report of burning sensation 3-7 days after test application. Reported reactions to the tape used in this study included strong irritation in two subjects and strong itching/burning in two subjects. However, since the final drug product does not contain the tape used in these studies, these tape-induced reactions are not relevant to the T.R.U.E. TEST final product. There were no deaths.

8. Advisory Committee Meeting

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

9. Other Relevant Regulatory Issues

No additional relevant regulatory issues were identified during the review of this supplement.

10. Labeling

Package Insert

The package insert (PI) was reviewed by the review committee, including the reviewer from the Advertising and Promotional Labeling Branch. All issues were acceptably resolved after exchange of information and discussions with the Applicant.

Carton and Container Labeling

All issues, including renumbering of the three panels from 1.2, 2.2, and 3.2 to 1.3, 2.3 and 3.3, respectively and addition of NDC numbers to the top third portion of the box and the foil were acceptably resolved after exchange of information and discussions with the Applicant.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The Committee recommends approval of the Applicant's BLA supplement.

b) Risk/benefit assessment

The data provided demonstrate that the reformulations of the potassium dichromate, neomycin sulfate, and fragrance mix allergen patches are safe and bioequivalent to the formulations of these patches in the currently approved T.R.U.E. TEST. In the case of the fragrance mix patch, clinical comparison of the current and reformulated patch to the reference preparation suggests that the reformulated fragrance mix PVP patch may provide a more sensitive and specific test than the fragrance mix HPC patch in the currently approved T.R.U.E. TEST.

c) Recommendation for Postmarketing Risk Management Activities

Not applicable.