

## Summary Basis for Regulatory Action Template

**Date:** November 12, 2015

**From:** Christina Houck, Chair of the Review Committee

**BLA/ STN#:** 103738/5129

**Applicant Name:** SmartPractice Denmark ApS

**Date of Submission:** January 23, 2015

**Review Goal Date:** November 23, 2015

**Proprietary Name/ Established Name:** T.R.U.E. TEST Thin-Layer Rapid Use Epicutaneous Patch Test

**Indication:** For use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 18 years of age and older whose history suggests sensitivity to one or more of the 35 substances included on the T.R.U.E. TEST panels

**Recommended Action:** Approval

**Signatory Authorities Action:** Approval

**Offices Signatory Authority:** Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, 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.

<b>Material Reviewed/ Consulted</b>	<b>Specific documentation used in developing the SBRA</b>	
<b>Reviewer Name – Document(s)</b>	<b>Date</b>	
Clinical Review	Kathleen Hise, MD	11/12/15
Statistical Review	Tammy Massie, PhD	10/1/15
CMC Review	Taruna Khurana, PhD	10/21/15
Methods Validation Review	Alfred Del-Grosso, Ph.D.	10/19/15

# 1. Introduction

T.R.U.E. TEST (Multiple Products: Allergen Patch Test Allergen Patch Test Kit) is 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 clinical 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 1.3, 2.3 and 3.3. Panel 1.3 contains 11 allergen patches and a negative control, Panel 2.3 contains 12 allergen patches, and Panel 3.3 contains 12 allergen patches. Each patch contains a specific allergen in a uniform gel coating on a polyester sheet.

On January 26, 2015 SmartPractice Denmark ApS (SmartPractice) submitted a supplement for a change in excipient for ethylenediamine dihydrochloride located in Panel 1.3. The Applicant provided Chemistry, Manufacturing and Controls (CMC) data and clinical bioequivalence data to support this change. The Applicant proposes to change the Package Insert to reflect this change. The provided change is as follows:

For the ethylenediamine dihydrochloride patch in Panel 1.3, the excipient will change from methylcellulose to povidone (PVP), while the concentration remains the same at 0.050mg per cm<sup>2</sup>.

## 2. Background

### Product Description

Allergic contact dermatitis (ACD) is caused by an allergen that elicits a Type IV 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, 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, 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. This supplement also 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.

In 2014, supplement STN 103738/5118 was approved for a change in excipient and dose strength for three allergens in panel 1.3, as well as the change in the declared labeled dose for Thiuram Mix.

### 3. Chemistry Manufacturing and Controls (CMC)

#### a) Product Quality

The basic manufacturing process for the ethylenediamine dihydrochloride patch is unchanged and involves [REDACTED]

[REDACTED]. In the current supplement, the Applicant proposes to change the vehicle from methylcellulose to PVP in the ethylenediamine dihydrochloride patch, with the dose remaining the same. The manufacturing process was verified by a process verification study where [REDACTED] batches of ethylenediamine dihydrochloride PVP gels were manufactured using [REDACTED]. Acceptance criteria for the relative standard deviation (RSD) were met when the manufactured gels and sheets were evaluated for homogeneity.

Stability studies of the new ethylenediamine dihydrochloride-PVP patch formulation were performed at 5°C and accelerated conditions of [REDACTED] for 24 months. Stability data from these studies support the proposed shelf life of 24 months (2 years) at 2-8°C for the new ethylenediamine dihydrochloride patch formulation.

(b) (4) [REDACTED] is used as the identity test for ethylenediamine dihydrochloride. [REDACTED] is the analytical method used for quantification of the amount of ethylenediamine dihydrochloride in each patch. The quantitative method was validated for specificity, linearity, accuracy, precision and robustness.

#### b) CBER Lot Release

No lots or issues are pending that would preclude approval of this supplement.

#### c) Facilities Review/Inspection

No ongoing or impending investigations or compliance actions with respect to SmartPractice's facilities or products are in effect. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management did not object to approval of this supplement.

### 4. Nonclinical Pharmacology/Toxicology

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

## 5. Clinical Pharmacology

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

## 6. Clinical/ Statistical

### a) Clinical Program

The supplement contained data from a single clinical bioequivalence study, SPD 12 P1401, to support the change in excipient for ethylenediamine hydrochloride, currently in Panel 1.3 of T.R.U.E. TEST, and changes in the labeling.

The study was an open label, prospective, single-center study designed to compare the bioequivalence of ethylenediamine dihydrochloride in the current vehicle, methylcellulose, to that of the allergen in a PVP formulation of T.R.U.E. TEST. The study enrolled 16 adult subjects, 18 years of age or older, with a clinical history of contact dermatitis and a current or previous (within the past ten years) positive patch test to ethylenediamine dihydrochloride. The assessment was based on concordance between positive patch test reactions to the two formulations of the allergen, as well as safety. The investigational allergen panel was applied at Visit 1 and was comprised of four patches, which consisted of two allergen and two negative control patches. The test panel was removed after 2 days at Visit 2. Subjects returned for Visit 3 on Day 3, Visit 4 on day 7, and Visit 5 on Day 21. The data were analyzed for reaction frequencies and concordance between the methylcellulose and PVP formulations of ethylenediamine dihydrochloride. The frequencies of late reactions, persistent local reactions, irritation, and any adverse events (AEs) were described and compared. Skin reactions to the panel were graded as negative, irritant reaction, doubtful reaction, weak positive, strong positive, or extreme positive.

For the evaluation of bioequivalence, a positive reaction was defined at either Visit 3 or Visit 4. The overall percent agreement between test results for the methylcellulose and PVP formulations of the allergen and Cohen's kappa statistic were calculated. A significant kappa value indicated that the observed agreement between formulations exceeded random chance.

For the Intent to Treat (ITT) Safety analysis population, the estimated percent agreement based on the observed response between methylcellulose and PVP formulations was 64.7% (95% CI = 38.4%, 85.8%). The computed Kappa statistic (0.23) for this ITT-Safety analysis population was not significant ( $p=0.35$ ). For the modified Intent to Treat (mITT) safety population, the percent agreement between methylcellulose and PVP formulations was 68.8% (11/16 subjects, 95% CI = 41.3%, 89.0%), and the kappa statistic was 0.31 ( $p$ -value  $P=0.29$ ), which is considered fair concordance. For the per-protocol (PP) population, the percent agreement between the two formulations was 68.8% (95% CI = 41.3%, 89.0%); the Kappa statistic (0.31) was not significant ( $p=0.29$ ).

**b) Pediatrics**

Under the Pediatric Research Equity Act (PREA) (section 505B of the Food, Drug, and Cosmetic Act [21 U.S.C. 355B]), PREA requirements do not apply to this application.

## **7. Safety**

Safety of the allergen ethylenediamine dihydrochloride in methylcellulose and PVP was assessed in the clinical bioequivalence study SPD 12 P1401. In this study, 3 of the 16 subjects enrolled experienced an adverse event, which were all resolved and not considered related to the study product. All three events were moderate in severity and non-serious.

## **8. Advisory Committee Meeting**

There were no issues pertaining to this supplement that required input from the Vaccines and Related Biological Products Advisory Committee.

## **9. Labeling**

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.

## **10. Recommendations and Risk/ Benefit Assessment**

**a) Recommended Regulatory Action**

The Committee recommends approval of this supplement to update the T.R.U.E. TEST package insert with the new excipient for Ethylenediamine Dihydrochloride.

**b) Risk/ Benefit Assessment**

Not Applicable.

**c) Recommendation for Postmarketing Risk Management Activities**

Not Applicable.

**d) Recommendation for Postmarketing Activities**

Not Applicable.