



Memorandum

DATE: February 22, 2016

TO: File, BLA 125579

FROM: Taruna Khurana, Ph.D. Regulatory Project Manager, Product Reviewer
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THROUGH: Ronald L. Rabin, M.D. Chief,
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APPLICANT: SmartPractice Denmark, Aps, U.S. License # 1888

SUBJECT: Product Review and Approval Recommendation Memorandum

REFERENCE: STN 125579 (Originally STN #103738/5031)

CROSS REFERENCES: IND 2466, BLA 103738/5031

Materials reviewed

103738/5031(January 5, 2006), 125579/000 Original BLA
125579/008 (August 19, 2014)
125579/011 (August 27, 2015)
125579/012 (October 21, 2015)
125579/014 (December 3, 2015)
125579/015 (January 15, 2016)

Summary/Background

SmartPractice Denmark ApS (SmartPractice) submitted a Biologics License Application (BLA) to add a Rubber Panel to their existing line of licensed T.R.U.E Test products. The Rubber Panel is an epicutaneous patch test indicated for use 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 five substances included in the Rubber Panel T.R.U.E. Test.

The Rubber Panel contains five rubber related allergen patches (Patch 2; Carba mix, Patch 3; Black Rubber mix, Patch 4; Mercaptobenzothiazole, Patch 5; Mercapto mix, Patch 6; Thiuram mix) and a (b) (4) negative control (Patch 1). All five rubber patches are currently on the approved T.R.U.E Test Panel 2.3. There is no change in the formulations of these rubber allergen patches and the firm states that no changes will be made to the already approved T.R.U.E. Test.

Regulatory background

SmartPractice's original submission (January 5, 2006) to add a stand-alone Rubber Panel to their licensed T.R.U.E. Test product line was classified by CBER as a Prior Approval Supplement (PAS) (STN 103738/5031). At the time of the original submission, the Applicant's name was Mekos Laboratories A/S (U.S. License 1623). The Applicant later changed their name to SmartPractice Denmark ApS (U.S. License 1888). On August 27, 2015, CBER re-classified SmartPractice's submission from a PAS to a BLA. CBER issued Complete Response (CR) letters and Applicant responses were as follows:

- CR Letter issued June 30, 2006
- Applicant response to CR submitted August 15, 2006
- CR Letter issued February 12, 2007
- Applicant response to CR submitted August 21, 2014
- CR Letter issued January 12, 2015
- Applicant response to CR submitted August 27, 2015

During the review phase of this BLA, additional regulatory approvals related to Rubber Panel allergen patches were issued. These approvals were:

- Mercaptobenzothiazole (August 8, 2012 approval of Mercaptobenzothiazole)
- Mercapto mix (April 24, 2014 approval of Mercapto mix)
- Thiuram mix (October 3, 2011 approval of Thiram mix and October 16, 2014 approval of label change of Thiuram mix from 25mcg/cm² to 27mcg/cm²)

Product review

SmartPractice's Rubber Panel consists of a piece of surgical tape (transparent (b) (4) film with medical acrylic adhesive 5.2 x13.0 cm) with 6 patches of 0.81 cm² (allergen gels applied over (b) (4)). Five of the six patches contain rubber related allergens and one serves as a negative control ((b) (4) patch). The panel is covered with a protective sheet and packed into an aluminum foil pouch. The pouch also contains a desiccant ((b) (4)) for moisture control. SmartPractice's other licensed T.R.U.E. Test panels are recommend for storage at 2 – 8 °C. However, the T.R.U.E. Test Rubber Panel is recommended for storage at room temperature ((b) (4) 25°C). The composition of each allergen patch of Rubber Panel is in table 1(adapted from the submission). All together 14 allergen substances are represented in Rubber Panel.

Table 1: Description of Rubber Panel Allergen Patches

Rubber Panel Allergens	Labeled Concentration	Allergen Components	Vehicle
Carba Mix	0.25 mg/cm ²	Diphenylguanidine (DPG) Zincdibutyldithiocarbamate (ZDB) Zincdiethyldithiocarbamate (ZDE)	Hydroxypropyl cellulose

Rubber Panel Allergens	Labeled Concentration	Allergen Components	Vehicle
Black Rubber Mix	0.075 mg/cm ²	N-isopropyl-N'-phenyl paraphenylenediamine Cyclohexyl-N'-phenyl paraphenylenediamine Diphenyl paraphenylene-diamine	Polyvidone
Mercaptobenzothiazol	0.075 mg/cm ²	Mercaptobenzothiazole	Polyvidone
Mercaptomix	0.075 mg/cm ²	N-cyclohexylbenzothiazyl- sulfenamide Dibenzothiazyl disulfide Morpholinylmercaptobenzothiazole	Polyvidone
Thiuram Mix	0.027 mg/cm ²	Tetramethylythiuram monosulfide Tetramethylthiuram disulfide Disulfiram Dipentamethylenethiuram disulfide	Polyvidone

I Information regarding source material specifications, drug substance, (b) (4) assays, and product stability was included in the January 2006 original submission. The product information in the original submission was reviewed by Dr. Bo Chi and can be found in her June 9, 2006. Deficiencies identified were included in the June 30, 2006 CR letter. One of the primary deficiencies identified was that the expiration dating of the rubber panel final product was not based on real time stability data of the final assembled product in the proposed new rubber panel configuration. Therefore, we requested stability data for the final assembled rubber panel product and for a commitment to perform stability studies through 24 months on the first three commercial batches (CR letter dated February 12, 2007). In their March 14, 2007 response to the CR letter, SmartPractice asked if they could submit stability data from their currently licensed T.R.U.E. Test panel 2.3, rather than their proposed new rubber panel configuration in order to establish expiry dating in support of approval. However, SmartPractice's licensed T.R.U.E. Test panel 2.3 consists of 5 rubber panel allergen patches and 7 other allergen patches; whereas the proposed new Rubber Panel T.R.U.E Test consists only of 5 allergen patches and a (b) (4) negative control. Because the two panels are configured differently, equivalency of stability data for expiration dating purposes could not be established. We did not agree to SmartPractice's proposal.

Source Material

Analytical reports and certificate of analysis (CoA) for each of the source material are provided. The analytical reports have identification and quantification methods used for testing purpose of raw materials. Source material lots are tested for identification, quantitation, and microbial count by in-house methods. The CoA of each lot contains all the information generated. The CoA is provided by the supplier of the raw material as well. The analytical report is generated by the Applicant. The information was reviewed and found acceptable. No additional details were included in this submission.

Drug Substance

SmartPractice defines the Drug Substance (DS) as (b) (4) with an individual allergen gel. The DS manufacturing process is summarized below. The manufacturing process used for the rubber panel allergens (Carba mix, Black Rubber mix, Mercaptobenzothiazole, Mercapto mix, and Thiuram mix) is the same as used in the manufacture of the currently licensed T.R.U.E. Test panels.

Manufacturing process of Rubber Panel allergen gel (b) (4) and patches

The Rubber Panel T.R.U.E. Test is manufactured in the same area as licensed T.R.U.E. Test panels 1.3, 2.3 and 3.3. There is no change in the manufacturing process and the formulation of Rubber Panel allergen patches. The procedures describing the T.R.U.E. TEST manufacturing process are provided in the BLA. The manufacturing process and process controls for each allergen patch have previously been reviewed and found acceptable therefore; only a summary of the manufacturing process is included in this memo.

(b) (4)

Process Validation - Allergen Gel (b) (4)

The process validation for manufacturing of the allergen gel (b) (4) is included in the BLA.

The allergen gel manufacturing process was validated for the following critical process steps:

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

Three batches of all allergen gel (b) (4) containing T.R.U.E Test Panel allergens were manufactured between (b) (4) in support of process validation. All of these batches included Rubber panel allergens as well. Manufacturing criteria were varied for the batches to capture extremes of the ranges.

Batch (b) (4): Normal Production settings

Batch (b) (4): Lowest values, shortest time, lowest (b) (4) settings

Batch (b) (4): Highest values, longest time, highest (b) (4) settings

Allergen gel (b) (4). The results were within validation acceptance criteria as indicated in Table 2 below.

Table 2: Process validation acceptance criteria

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

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

Process validation of gel (b) (4)

The allergen gel manufacturing process was also validated for T.R.U.E. Test panels in 2001. Three batches of 11 selected allergens were prepared for the validation of (b) (4). Three of these were components of rubber panel (Carba mix, Mercaptobenzothiazole, and Mercapto mix). The process validation demonstrated (b) (4) of the gel (b) (4) and all the batches met the acceptance criteria of (b) (4).

Validation of the drying process

The drying procedure of the gel (b) (4) was validated in 2001 for T.R.U.E. TEST panels. Three batches of allergen (b) (4) were manufactured for the drying process validation. The results for (b) (4) remain within acceptance criteria under all tested drying conditions. No deviations were noted for the tested allergens of the Rubber Panel.

Drug product

SmartPractice defines the DP as a Rubber Panel containing 5 allergen patches (indicated above) and a negative control patch is drug product. Each allergen patch has a surface area of 0.81 cm². The composition of each allergen patch is indicated in Table 1 of this memo and release specifications are provided in Table 3.

Manufacturing of the Rubber Panel Drug Product

The allergen gel (b) (4) (DS) are (b) (4) out into allergen gel patches (0.9 cm x 0.9 cm). The patches are placed onto predefined locations on the surgical tape. The tape is marked with panel orientation arrow and covered with protective foil. The tape is cut into test panels. The panels are packed into labeled laminated foil pouches. The laminated pouches are (b) (4) for sealing. The sealed foil pouch is placed in a plastic wrapped with reading guide and sealed. This sealed plastic wrap is packed into labeled cartons. Each patch is tested by specific analytical method and contains (b) (4) of its labeled value at the release.

The final panels are stored at room temperature. Final patches are tested for identification, Quantitative Analysis, and Content Uniformity.

Analytical methods for allergen (b) (4) and allergen patch

The analytical methods for identification and quantification of Rubber Panel allergen (b) (4) and allergen patches are the same as used for the Rubber allergens in the licensed T.R.U.E. TEST.

- Carba mix (07397)-The patch is (b) (4)
- Black rubber mix (07393)-The patch is (b) (4)
- Mercaptobenzothiazole (07383)- The patch is (b) (4)
- Mercapto mix (07396)- The patch components are (b) (4)

- Thiuram mix (07368)-The patch is (b) (4)

Analytical methods are validated for (b) (4), specificity ((b) (4)), linearity, detection and quantification limit, accuracy ((b) (4)), precision (repeatability and intermediate precision), and robustness (varying assay conditions). The validation results were within acceptance criteria for all the allergens.

On January 7, 2015 SmartPractice submitted a revised Carba mix analytical method and validation report as a PAS to their BLA for their licensed product (STN 103738/5128). The supplement included modifications to the analytical method for Carba mix. The release specifications for Carba mix remained unchanged at 0.25 mg/cm² (b) (4) with a range of (b) (4). The validation data and report was reviewed and approved on July 7, 2015 (103738/5128). The optimized analytical method was found to be adequately validated for its intended use for identification and determination of DPG, ZDE, and ZDB concentration in Carba mix patch of T.R.U.E. Test. The changes in the Carba mix analytical method are applied to new rubber panel through cross reference.

The release specifications for the revised Carba mix rubber allergen gel sheets and all other rubber panel allergen gel sheets are provided below.

Table 3: Release specifications of Rubber Panel Allergen Gel (b) (4)

Allergen	Tests	Release limits (mg/cm ²)
Carba Mix	Transparent colorless or almost colorless	(b) (4)
Black Rubber Mix	Transparent yellowish brown	(b) (4)
Mercaptobenzothiazole	Transparent colorless or almost colorless	(b) (4)
Mercapto Mix	Transparent colorless or almost colorless	(b) (4)
Thiuram	Transparent colorless or almost colorless	(b) (4)
Negative Patch	Transparent colorless	Not detected
Content Uniformity for (b) (4)	(b) (4)	(b) (4)

Allergen	Tests	Release limits (mg/cm ²)
Content Uniformity for (b) (4)	(b) (4)	(b) (4)
Microbial Test	(b) (4) microorganisms/test Absence of (b) (4) Absence of (b) (4)	Yes Yes

Stability Study of the Rubber Panel (Doc No. 11108, September 6, 2011)

Three production batches ((b) (4)) of rubber panel manufactured using production size equipment were stored under the following conditions for stability studies:

- 25°C/(b) (4) RH for 24 months (0, 3, 6, 9, 12, 18, and 24)
- (b) (4)

Samples were obtained at indicated time points for appearance (color and transparency), chemical analyses, and microbiological testing. All the patches remained within predefined acceptance limits after 24 months of storage at 25°C (b) (4).

The negative control patch (position 1) was tested for the absence of active allergen substances included in five allergen patches. The results indicated no migration of any of the active allergen substance in the negative control patch at 25°C (b) (4) of storage. Based on this data the sponsor plans on testing negative control patch during release testing only.

Based on the stability data for visual inspection, quantitative chemical assays and microbial testing ((b) (4)), and specified organisms) the rubber panel expiration date is 24 months when stored at or (b) (4) 25°C.

The Applicant also commits to perform stability testing first three commercial batches at 25°C/ RH for 24 months and at (4). This is acceptable.

The Rubber Panel T.R.U.E. Test is categorized as a combination product under 21 CFR 3.2(e), and therefore is subject to both the CGMP regulations (21 CFR part 211) and the Devices Quality System Regulations (QSR) (21 CFR part 820). SmartPractice has performed a GAP analysis of the current Quality System including Management responsibilities (§820.20), Design controls (§820.30), Purchasing controls (§820.50), and Corrective and Preventive action (§820.100). For Quality System Requirements for the device component of the Rubber Panel

T.R.U.E. Test please see Richard Heath Coat's (OCBQ/DMPQ) memo and year 2016 surveillance inspection report and memo.

Product Information Request

Product issues and findings identified during the review of the submitted files were transmitted to the firm on January 12, 2015 in an Information Request (IR). The responses received from the firm on August 27, 2015 are in italics. The final acceptability of the Applicants IR responses are noted in bold below.

1. Please update the concentration of Thiuram mix from 25 µg/cm² to 27 µg/cm² throughout your submission and package insert, based on your recent approval of STN 103738/5118.

SmartPractice: Thiuram mix concentration changed from 25 ug/cm² to 27 ug/cm² throughout the submission and Package insert.

Reviewer: The response is acceptable.

As the review process continued additional issues were identified and communicated to the firm as IR on September 30, 2015. The responses received from the firm on October 21, 2015 are in italics. The final acceptability of the Applicants IR responses are noted in bold below.

2. Please provide legible copies of executed batch records for the manufacture and assembly of Rubber Panel T.R.U.E. TEST.

SmartPractice: Packing instruction batch journal and batch records of manufacturing and assembly of Rubber Panel T.R.U.E. TEST is provided.

Reviewer: The response is acceptable.

Additional product related issues and findings identified during the review of the submission were transmitted to the firm on November 13, 2015 as an Information Request. The responses received from the firm on December 3, 2015 are in italics. The final acceptability of the Applicants IR responses are noted in bold below.

3. Section 7.4.4, Manufacturing Process Flow, submitted on August 27, 2015 in response to Question #6, lists a storage condition of (b) (4) for the allergen (b) (4) and the finished rubber panel. Stability study of the rubber panel was conducted at 25°C/(b) (4) RH and the recommended storage condition for the panel is (b) (4) 25°C in your submission. Please clearly state the storage conditions for the allergen (b) (4) and the finished Rubber Panel.

SmartPractice: The storage condition for the allergen (b) (4) are (b) (4) as listed. It is a mistake that the finished rubber panel is listed to be stored at (b) (4). The finished rubber panel has to be stored (b) (4) 25°C as written in the submission.

Reviewer: The response is acceptable.

4. Please indicate the chemical assays and tests used for determining rubber panel allergens during the stability studies.

SmartPractice: The chemical assay methods used during stability studies are reported in "Stability Study of Rubber Panel" submitted September 6, 2011. Due to revalidation of the analytical methods used for analyses of the allergens in Rubber Panel, new numbers have been assigned to the methods. The new methods are comparable with the methods used in the stability studies. The updated method numbers are in quality specification for Rubber Panel submitted in relation to updated analytical method for determination of Carba mix.

Reviewer: The response is acceptable. The updated method numbers were located in Carba mix analytical method report.

Information request was communicated to the firm on December 11, 2015. The response received from the firm on January 15, 2016 is in italics. The final acceptability of the Applicants IR responses are noted in bold below.

5. As this product is under review as a separate Biological License Application than the approved T.R.U.E. TEST, STN 103738, please submit the analytical methods and validations for the five component assays for inclusion in this license file, including the finished product assays and validations for Carba mix, Black Rubber mix, Mercaptobenzothiazole, Mercapto mix and Thiuram mix.

SmartPractice: Analytical methods and validations are provided for Carba mix, Black Rubber mix, Mercaptobenzothiazole, Mercapto mix and Thiuram mix.

Reviewer: The response is acceptable.

Recommendation:

Based on a complete review of all product information and data from the original BLA submission and all amendments listed on the first page of this memo, I recommend approval of SmartPractice Denmark's Rubber Panel T.R.U.E. TEST.