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Subject: DBSQC Primary Review Memo: BLA for Thin-Layer Rapid Use Epicutaneous, (T.R.U.E. Test) Patch Test, Rubber Panel, STN 125579/0

To: File: STN 125579/0

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Recommendation: Approvable with respect to analytical procedures used for identity, product content and product uniformity

Summary

SmartPractice is submitting an application to market a new panel containing five rubber related allergen patches (Carba Mix, Black Rubber Mix, Mercaptobenzothiazole, Mercapto Mix, and Thiuram Mix) plus a negative control. These components are currently on the approved T.R.U.E. Test panel 2 (Carba Mix, Black Rubber Mix, Mercapto Mix and Thiuram Mix) and Test Panel 3 (Mercaptobenzothiazole). Identical formulations will be used on this new panel. No changes are being proposed in this submission to the existing approved panels that will continue to be marketed under STN 103738..

Analytical procedures and validations for this rubber panel product are identical to those currently used with the rubber related patch components of the approved STN 103738. The approved T.R.U.E. Test product contains 35 component patches that are configured in 3 separate panels of twelve patches, including one negative blank patch. In an IR of 12/11/2015, it was requested that since this product was under review as a separate BLA, analytical methods and validations for the five component assays relevant to this submission be submitted for inclusion in STN 125579. These were satisfactorily provided on 01/15/2016.

Review Narrative

Materials Reviewed

103738/5031 Original Submission
125579/12 Attachment 1b: Batch Records
125579/14 Attachment 5: Batch Records
125579/15 Analytical Methods and Validations

This submission was originally received as a prior approval supplement (103738/5031) to the original T.R.U.E. Test BLA on January 5, 2006. The name of the firm at the time was Mekos Laboratories AS (License 1623). The firm's name was subsequently changed to SmartPractice Denmark, ApS prior to the resubmission of this file.

A Complete Response Letter was issued to the firm on February 12, 2007. Analytical procedures and validations were not issues in this CR letter. CBER notified the Sponsor on June 7, 2013 that this supplement would be converted to a new BLA, largely due to the difficulty of tracking two products with different package inserts under the same STN. The firm provided responses to the Complete Response Letter on August 19, 2014.

T.R.U.E. Test Rubber Panel is a ready-to-use patch test. Each panel consists of a piece of surgical tape with 12 polyester patches. Five of the six patches contain a specific allergen, while one of the six patches serves as a negative control. A protective sheet covers the panel. It is packed into pouches of laminated aluminum foil. A desiccant paper is enclosed with each pouch. The firm states this newly configured panel requires no refrigeration and exhibits a room temperature shelf life of 24 months based on stability studies.

The T.R.U.E. Test Rubber Panel is a five component subset of allergens from the currently approved product. The original T.R.U.E. Test was approved in 1994.

This application covers a new presentation of Carba Mix, Black Rubber Mix, Mercaptobenzothiazole, Mercapto Mix, Thiuram Mix, as well as a negative control that consists of a (b) (4) vehicle.

The manufacturing facility for the T.R.U.E. Test Rubber Panel is located in Hillerod Denmark. Originally, the company was named Pharmacia and Upjohn. The company's name was changed to Mekos Laboratories ApS in 2006 and subsequently to SmartPractice Denmark ApS. The location and manufacturing site of the firm has remained the same.

Specifications for the Rubber Panel and associated test methods for Drug Product identification and assay are as follows:

Table 1. Test Methods for Identification.

Patch No.	Allergen	Appearance	Allergen Identity
1	Negative Control	Transparent, colorless patch	
2	Carba Mix	Transparent, colorless or almost colorless patch	Pass identification of carba mix per Test Method 07397
3	Black Rubber Mix	Transparent, yellowish brown patch	Pass identification of black rubber mix per Test Method 07393
4	Mercaptobenzothiazole	Transparent, colorless or almost colorless patch	Pass identification of mercaptobenzothiazole per Test Method 07383
5	Mercapto Mix	Transparent, colorless or almost colorless patch	Pass identification of mercapto mix per Test Method 04774
6	Thiuram Mix	Transparent, colorless or almost colorless patch	Pass identification of thiuram mix per Test Method 03945

Table 2. Test Methods for Assay

Test/Characteristic	Release Limits	SOP #
Assay of Carba Mix labeled amount: 0.25 mg/cm ²	(b) (4)	07397
Assay of Black Rubber Mix labeled amount: 0.075 mg/cm ²	(b) (4)	07393
Assay of Mercaptobenzothiazole labeled amount: 0.075 mg/cm ²	(b) (4)	07383
Assay of Mercapto Mix labeled amount: 0.075 mg/cm ²	(b) (4)	07396
Assay of Thiuram mix labeled amount: 0.025 mg/cm ²	(b) (4)	07368
Content uniformity	(b) (4)	(b) (4)

Test/Characteristic	Release Limits	SOP #
Content Uniformity	(b) (4)	(b) (4)
Microbial total count	Maximum of (b) (4) microorg/test	03672
Absence of (b) (4)	Pass	05094
Absence of (b) (4)	Pass	05095

Chemical Test Methods

Carba Mix (Patch No. 2) is determined as described in SmartPractice SOP 07397-02. Carba mix is (b) (4) and the component compounds diphenylguanidine, zinc diethyldithiocarbamate and zinc dibutyldithiocarbamate determined by (b) (4). Sample concentration is calculated against a series of standards prepared from designated standard substances of these compounds. The same method is used for identification. Method validation was submitted under STN 103738 as Doc. No. 13183. The method and validation were previously reviewed and approved as a supplement under STN 103738.

The assay of Black Rubber Mix (Patch No. 3) is described in SmartPractice SOP 07393-01. Patches are (b) (4) and components determined by (b) (4). Sample concentration is calculated against a series of standards made from the standard substances of the component compounds N-isopropyl-N'-phenylparaphenylenediamine (IPPD), N-cyclohexyl-N'-phenylparaphenylenediamine (CPPD) and N,N'-diphenyl paraphenylenediamine (DPPD). The same method is used for identification. Method validation was submitted under STN 103738 as Doc. No. 13183. The method and validation were previously reviewed and approved as a supplement under STN 103738. Method validation was submitted under STN 103738 as Doc. No. 12176. The method and validation were previously reviewed as a supplement under STN 103738.

Mercaptobenzothiazole (Patch No. 4) is determined according to SmartPractice SOP 07383-04. Mercaptobenzothiazole is (b) (4)

Quantitation is against a series of standards prepared from a designated standard substance. The same method is used for identification. The method and validation (Doc. No. 11168) were previously reviewed and approved as STN 103738 supplement.

Mercapto mix (Patch No. 5) is determined using SmartPractice SOP 07396-03. Mercapto mix consists of morpholinyl mercaptobenzothiazole (MMBT), N-cyclohexylbenzothiazyl sulphenamide (CBS) and dibenzothiazyl disulphenamide (DBTD). These three components are (b) (4) and determined by (b) (4). Designated standard substances are used to prepare a

series of standards. The same method is used for identification. The method and validation (Doc. No. 13181) were previously reviewed and approved as a supplement under STN 103738.

The assay of Thiuram mix (Patch No. 6) is described in SmartPractice SOP 07368-04. Thiuram compounds are (b) (4) and determined by (b) (4). Tetramethylthiuram disulphide (TMTD) standard substance is used to prepare a series of standards. The same method is used for identification. The method and validation (Doc. No. 09146) were previously reviewed and approved as a supplement under STN 103738.

All of the SOPs and Validation Reports associated with the 5 Rubber Panel patch materials were submitted to STN 125579 as Amendment 15. This was in response to a CBER IR of 12/11/2015.

Microbiological Test Methods

The Microbial Total Count of Patches Test Method (Method No: 03672-13, Dated Oct 2003) was submitted with the original T.R.U.E. Test application. Methods for testing for the presence of (b) (4) and (b) (4) are also as described in the currently licensed T.R.U.E. Test product.

Conclusion

Analytical procedures and validations described for STN 125579, T.R.U.E. Test Rubber Panel are unchanged from those previously approved for STN 103738, T.R.U.E. Test. This BLA is approvable regarding the analytical methods used for identification, assay consistency and product uniformity.