



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Biologics Evaluation and Research  
10903 New Hampshire Ave  
Building 71, G112  
Silver Spring, MD 20993-0002

**To:** Administrative File: STN 125579/0

**From:** Richard Heath Coats, CMC Facility Reviewer, CBER/OCBQ/DMPQ/BI

**Through:** Carolyn Renshaw, Branch Chief, CBER/OCBQ/DMPQ/BI

**CC:** Elizabeth Valenti, Chairperson, CBER/OVRR/DVRPA/CMC1  
Christina Houck, RPM, CBER/OVRR/DVRPA/CMC1

**Subject:** Primary Review Memo: BLA for Thin-Layer Rapid Use Epicutaneous (TRUE) Patch Test Rubber Panel

**Product** Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test

**Indication:** Patch test for the diagnosis of contact dermatitis

**Applicant:** SmartPractice Denmark ApS US License 1888  
Herredsvejen 2  
3400 Hillerod Denmark  
Registration Number 3003216248

**Recommendation:** Complete Response – Deficiencies listed below

**Due Date:** February 20, 2015

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**Complete Response Letter Deficiencies**

1. Please confirm the areas used for TRUE TEST Rubber Panel are the same manufacturing areas as previously licensed for TRUE TEST panels. Please indicate if any changes have been made to the manufacturing areas, equipment, or processes for the Rubber Panel since the original submission of this material. If changes have been made, please provide a summary of the change and any testing performed to assess the adequacy of the change.
2. Please indicate if any changes have been made to the provided flow diagrams for the Rubber Panel since the original submission of this material.

3. Please provide the current procedure for the assembly and pouch packing of the TRUE TEST Rubber Panel. Information originally submitted appears to be for assembly of the original three panel TRUE TEST.
4. Please indicate if an assembling automation validation was executed for the TRUE TEST Rubber Panel. It appears that the assembling automation validation provided in the submitted materials is for the one of the original TRUE Test panels.
5. Please indicate if (b) (4) water is still utilized in product manufacture.
6. Please provide an environmental assessment or a request for categorical exclusion according to 21 CFR 25.31.

### **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. All of these rubber related patches are currently on the approved T.R.U.E TEST panel 2.1, and the identical formulation will be used on this new panel. The firm states that no changes will be made to the existing approved panels.

This submission was originally received as a paper submission as a prior approval supplement to the original TRUE Test BLA STN 103738 on January 5, 2006 (103738/5031). The name of the firm at the time was Mekos Laboratories AS (License 1623). The submitted material consisted of the following documents:

### **Cover Letter**

### **Application Form 356(h)**

### **Chemistry Manufacturing and Controls**

### **Establishment Description**

### **Attachment 0** Rubber Panel Rationales

### **Attachment 1** T.R.U.E. TEST Rubber panel, proposed labelling; box, template and foil

### **Attachment 2** Insert

2.1 current T.R.U.E. TEST® panel 1.1 and 2.1 Package Insert

2.2 proposed T.R.U.E. TEST® Rubber panel Package Insert

### **Attachment 3** Certificate of Incorporation.

### **Attachment 4** Organization Chart.

### **Attachment 5** Site plan.

### **Attachment 6** Companies situated in the building

### **Attachment 7** SOP 052. Cleaning of rooms .for preparation and packing of T.R.U.E. TEST and equipment in these rooms.

### **Attachment 8** Ventilation plant.

### **Attachment 9** HVAC System.

### **Attachment 10** Flow diagrams.

10.1 raw materials

10.2 product

- 10.3 personnel
- 10.4 equipment
- 10.5 waste

**Attachment 11** Source material specifications and certificates

**Attachment 12** SOP 036. General working instruction of T.R.U.E. TEST® preparation. (English translation).

**Attachment 13** SOP 139. The receipt, sampling, approval/rejection of T.R.U.E. TEST® raw materials and packing materials (English translation).

**Attachment 14** Flow diagrams

14.1 diagram - production

14.2 Flow chart of T.R.U.E. TEST® production

**Attachment 15** Example of Manufacturing Methods

**Attachment 16** Examples of Manufacturing Procedure/batch journal for sheets

**Attachment 17** Process validation

- Process validation of [REDACTED]
- Process validation of gel (b) (4)
- Validation of the drying process
- Microbiological cleaning validation

**Attachment 18** Stability Study Report +

**Attachment 19** Specification for Rubber Panel sheets

**Attachment 20** Methods of analysis for the drug substance ([REDACTED])

**Attachment 21** Composition of the drug product

**Attachment 22** Specifications for Rubber Panel, drug product

**Attachment 23** Assembling Automaton validation report

**Attachment 24** Microbiological test methods

**Attachment 25** Container/closure specifications and test methods

**Attachment 26** Validations reports

**Attachment 27** SOP 44. Monitoring [REDACTED] water for microbiological and chemical control in the production area (English translation).

**Attachment 28** Water in production (b) (4).

**Attachment 29** SOP 082. Monitoring of particles in special areas in zone (b) (4).

**Attachment 30** SOP 926. Microbial environmental monitoring of T.R.U.E. TEST premises.

**Attachment 31** SOP015 Technical and medical complaints

**Attachment 32** SOP450 Procedures for adverse events

A Complete Response Letter was issued to the firm on February 12, 2007 for this submission. CBER communicated to the firm in June 2013 that this PAS submission would be converted to a new BLA. The firm provided responses to the Complete Response Letter on August 19, 2014. At some point in time between 2012 and 2014 the firm changed its name from Mekos Laboratories AS to SmartPractice Denmark ApS (License 1888).

A reviewer from DMPQ was not originally assigned to this file when submitted in 2006. I was assigned to review this submission on November 10, 2014. There were no facilities or equipment comments noted in the Complete Response Letter, therefore, this memorandum provides a review of the originally submitted materials. The originally submitted materials are almost identical to materials reviewed by D Kearns of DMPQ in his review of STN 103738/5074. The

mentioned submission was a Prior Approval Supplement for addition of new allergens to the licensed TRUE Test. A majority of items in this submission have been reviewed by Kearns previously and therefore will not be reviewed again in this memorandum.

### **Introduction**

TRUE Test Rubber Panel is a ready-to-use patch test. Each panel consists of a piece of surgical tape with 6 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 TRUE Test Rubber Panel is a subset of allergens from the original product, TRUE Test. The original TRUE Test was approved in 1994.

The approved T.R.U.E. TEST® product, STN 103738, is a ready to use patch test system containing 23 of the most common allergens suspected of causing allergic contact dermatitis and a negative control.

Nickel Sulfate	p-tert-Butylphenol Formaldehyde Resin
Wool Alcohols	Epoxy Resin
Neomycin Sulfate	Carba Mix
Potassium Dichromate	Black Rubber Mix
Caine Mix	CI+Me-Isothiazolinone (Kathon® CG)
Fragrance Mix	Quaternium-15
Colophony	Mercaptobenzothiazole
Paraben Mix	p-Phenylenediamine
Negative Control	Formaldehyde
Balsam of Peru	Mercapto mix
Ethylenediamine Dihydrochloride	Thimerosal (Thiomersal)
Cobalt Dichloride	Thiuram Mix

Each panel consists of a surgical tape with 12 polyester patches. The allergen-containing patches are coated with a gel layer containing a uniformly dispersed specific allergen or allergen mix. The test panel is covered by a protective sheet and sealed in a pouch of laminated foil. A desiccant paper is included in the Panel 2.1 package for stability purposes.

This application covers a new presentation of Carba Mix, Black Rubber Mix, Mercaptobenzothiazole, Mercapto Mix, Thiuram Mix, and a negative control, present at TRUE TEST panel 2.1 (negative control on Panel 1.1).

The manufacturing facility for the TRUE Test Rubber Panel is located in Hillerød Denmark. Originally, the company was named Pharmacia and Upjohn as noted in RMS/BLA. The company's name changed to Mekos Laboratories ApS as noted in the materials submitted for this file in 2006. The firm's name has since changed to SmartPractice Denmark ApS. The FEI number 3003216248 is assigned to both Mekos and SmartPractice. The address for the facility

has remained the same regardless of the company name. RMS/BLA was corrected to note the name of SmartPractice ApS in the facility information.

Allergens were added to the TRUE Test product through the creation of a third panel. Allergens were added to the product in 2007 (STN 103738/5019 Approved June 5, 2007) and in 2011 (STN 103738/5074 Approved February 29, 2012).

There is no significant new manufacturing information presented for the five allergens that will constitute the Rubber Panel. Documentation presented to support this submission was previously reviewed by DMPQ as noted in the review of STN 103738/5074 performed by D Kearns in 2011.

The firm states that all of the rubber patches proposed for the TRUE Test Rubber Panel use identical formulations as on the currently approved TRUE Test panel 2.1. The rooms used to manufacture the TRUE Test Rubber Panel are the same areas used to manufacture the currently licensed TRUE Test product, panels 1.1, 2.1, and 3.1.

The Hillerod Denmark facility was inspected by ORA in January 2014 and designated VAI. The inspection of SmartPractice to support this BLA will be waived based on the January 2014 inspection.

#### **Environmental Assessment (Exclusion)**

An environmental assessment or a request for categorical exclusion for filing an Environmental Impact Analysis was not provided with the submitted materials for this application. Refer to Complete Response Letter Deficiency #6 on page 2 of this memo.

The firm requested a categorical exclusion for the currently licensed TRUE Test in STN 103738/5074 based on 21 CFR 25.31(b) – “if an action increases the use of an active moiety but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.”

#### **Product Indications**

The TRUE Test Rubber Panel is a patch test containing five rubber allergens used for diagnosis of allergic contact dermatitis.

The test panel is typically applied to the skin of the upper back. The humidity of the skin hydrates the film and transforms to a gel, allowing the allergen to migrate to into the skin, thereby reaching the cells of the immune system. The test is removed after 48 hours and read at 72-96 hours after the application, when the allergic responses are fully developed and mild irritant reactions have faded. Additional readings at 1 week and 21 days after panel placement are also advised in some cases.

#### **Product Description**

The Rubber Panel consists of a surgical tape with 6 polyester patches. The five allergen-containing patches are coated with a gel layer containing a uniformly dispersed specific rubber allergen or allergen mix. The sixth patch is a negative control. The test panel is covered by a

protective sheet and sealed in a pouch of laminated foil. A desiccant paper is included in the package for stability purposes.

### **Manufacturing Process Description**

There is no change to the manufacturing process for the five allergen and one negative control patches proposed for the Rubber Panel. The only difference is the Rubber Panel product will consist of one panel containing six patches, while the currently licensed TRUE Test consists of three panels with 12 patches on each panel.

Dan Kearns reviewed the manufacturing process for panels in his review of STN 103738/5074, and so a summary will only be provided here.

Allergens/allergen mixes are incorporated in exact dosage in a hydrophilic gel. The allergen-gel preparation is coated on an impermeable backing of polyester and dried to a thin film. The coated (b) (4) is then cut into 9mm X 9mm squares (test patches), which are mounted on tape forming a standard test panel.

### **Allergen Gel (b) (4) Drug Substance**

#### ***Raw Materials***

The materials used to manufacture each Rubber Panel allergen or allergen mix are a subset of the same materials used to currently manufacture the licensed TRUE Test. Quality specifications are provided for the rubber allergens used in the Rubber Panel. A Chemical Analytical Requisition and Report for Raw Material, along with a certificate of analysis, is provided for each material that indicates the testing performed and the result. SOP 139 *The receipt, sampling, approval/rejection of T.R.U.E. TEST raw materials and packing materials* is provided was reviewed and found acceptable previously by Kearns.

Raw materials used to prepare each allergen or allergen mix for the Rubber Panel are listed as follows:

Carba mix consists of: Diphenylguanidine, Zincdiethyldithiocarbamate and Zincdibutyldithiocarbamate (1: 1:1)

Black rubber mix consist of: N-isopropyl-N'-phenyl paraphenylenediamine, N-cyclohexyl-N'-phenyl paraphenylenediamine and N, N'-diphenyl paraphenylenediamine (2:5:5).

Mercaptobenzothiazole consists of only Mercaptobenzothiazole.

Mercapto mix consists of: Morpholinylmercapto-benzothiazole, N-cyclohexylbenzothiazyl-sulphenamide and Dibenzothiazyl disulphide (1 :1 :1 ).

Thiuram mix consists of: Tetramethylthiuram monosulphide, Tetramethylthiuram disulphide, Disulfiram (tetraethylthiuram disulphide) and Dipentamethylenethiuram disulphide (1 :1:1:1 ).

The firm provided SOP 139, *The Receipt, Sampling, Approval/Rejection of T.R.U.E. TEST Raw Materials and Packing Materials*. This SOP is dated 2004 and has not changed since prior reviews of TRUE Test.

### ***Manufacturing Description***

A detailed review of the manufacturing description will not be provided since the process of manufacturing the Rubber Panel is the same as the approved TRUE Test. SOP 036 *General Work Instruction of TRUE TEST preparation* is provided in the submitted material. The work instruction provided is from 2001, indicating that this procedure was reviewed by Kearns in review of STN 103738/5074. Kearns describes the manufacturing process in his review and it follows this procedure.

The allergen [REDACTED] is the drug substance. The manufacturing procedure for the Carba Mix, Black Rubber Mix, Mercaptobenzothiazole, Mercapto Mix and Thiuram Mix allergen (b) (4) are equal to the manufacturing procedures for the currently licensed TRUE Test.

The manufacturing methods for each specific allergen gel drug substance are provided in the submitted materials. The methods list the active substances and the concentration of each substance in a patch. These processes have been previously reviewed so the next paragraph provides a general summary of the manufacturing process.

Each allergen or allergen mix utilized in the Rubber Panel is incorporated into formulation of a gel, and the gel is then applied to a polyester sheet. Gel coated polyester (b) (4) are then (b) (4) [REDACTED]. (b) (4) are covered with protective foil then trimmed to specifications. Five trimmed (b) (4) are packed into a foil pouch and closed by (b) (4) for storage until further manufacture. The target batch size for the gel recipe is (b) (4) which correlates to a quantity of (b) (4) for each allergen.

Manufacturing flow diagrams for raw materials, product, personnel, equipment, and waste, are provided with the submitted material and are dated 2004. These are the same flow diagrams reviewed by Kearns in 2011. Complete Response Letter Deficiency #2 on page 1 of this review requests the firm to confirm these flow diagrams are current and unchanged.

### ***In-Process Controls***

In-Process control testing is performed to determine that the rubber allergens meet the concentration specifications for each patch on the panel. This testing is the same as for these allergens present in the licensed TRUE Test, and the in-process specifications are presented in the table below:

Test/Characteristic	Release Limits	Test Method
In-process of carba mix labeled amount: 0.25 mg/cm <sup>2</sup>	(b) (4)	04786
In-process of black rubber mix labeled amount: 0.075 mg/cm <sup>2</sup>	(b) (4)	04775
In-process of mercaptobenzothiazole	(b) (4)	04773

Test/Characteristic	Release Limits	Test Method
labeled amount: 0.075 mg/cm <sup>2</sup>	(b) (4)	
In-process of mercapto mix labeled amount: 0.075 mg/cm <sup>2</sup>	(b) (4)	04774
In-process of thiuram mix labeled amount: 0.025 mg/cm <sup>2</sup>	(b) (4)	03945
In-process controls	(b) (4) (b) (4)	(b) (4) (b) (4)

(b) (4) patches for each allergen are tested for in-process control testing.

#### ***Process Validation of Production***

The (b) (4) production process validation for the entire TRUE TEST panel is included in the submitted material. Assembling and packaging of the finished product is not included in this process validation.

The five allergens present on the TRUE TEST Rubber Panel were included in this process validation for the currently licensed product.

#### ***Batch Summary***

Validation batch No.1 (b) (4) -normal production.

Validation batch No. 2 (b) (4) - is produced on the basis of the lowest values in manufacturing procedure, which means the shortest time, the minimum preparation, the lowest (b) (4) within the established limits in the current Master Batch Record.

Validation batch No. 3 (b) (4) - is produced on the basis of the highest values of the manufacturing procedure, which means the longest time, the maximum preparation, the highest (b) (4) within the established limits in the current Master Batch Record.

The (b) (4) were manufactured in the period (b) (4) and the document notes all operators participated in the production.

There were no deviations documented for any of the rubber panel allergens, nor were any deviations noted that were applicable to the general gel manufacturing process.

#### ***Process Validation of Gel (b) (4)***

This process validation was executed for the original TRUE TEST panels in 2001. This validation was executed to show that the gels manufactured according to the manufacturing procedures are (b) (4) of allergen immediately before (b) (4) production of the gel.



3 batches of 11 selected allergens are validated. The gels are produced for this validation and not for commercial production. Three of the selected allergens for this process validation are components of the proposed Rubber Panel (Carba Mix, Mercaptobenzotia, and Mercapto Mix).

The process validation demonstrated that gel (b) (4) are (b) (4). There were no deviations noted for the allergens tested that are part of the proposed Rubber Panel.

### ***Validation of the Drying Process***

This process validation was executed for all allergens in the TRUE TEST Panel

Three (b) (4) were manufactured for each allergen. Each allergen (b) (4) had a limit for (b) (4) after the drying process is completed. The (b) (4) acceptance criteria was met for all five allergens in the proposed Rubber Panel. There were no deviations noted pertaining to any of the five proposed Rubber Panel Allergens

### **Rubber Panel Drug Product**

The allergen coated polyester (b) (4) are cut into patches and placed in a specified location on a piece of self-adhesive surgical tape (b) (4). A protective sheet of (b) (4) covers the (b) (4) and then it is packed in a pouch of packaging laminate. A desiccant paper is enclosed in the pouch.

A vision system is used to verify that tapes are assembled correctly.

### ***Product Composition***

The Rubber Panel consists of a total of six patches on a piece of self-adhesive surgical tape (b) (4). One of the patches is a negative control. The five patches remaining contain one of the following rubber allergens:

- Carba mix
- Black rubber mix
- Mercaptobenzothiazole
- Mercapto mix
- Thiuram mix

Each patch is 9mm x 9mm for a surface area of 0.81cm<sup>2</sup>.

Ancillary components for the allergens on rubber panel are identical with components for the licensed TRUE Test-panel 1.1, 2.1 and 3.1. The carrier materials are uncolored (b) (4) sheets. The self-adhesive (b) (4) is comprised of a (b) (4) support. The adhesive is (b) (4). The finished tape is covered with a protective sheet made of (b) (4) on one side. The packing laminate is a (b) (4).

### ***Rubber Panel Specifications***

Release testing for the Rubber Panel is provided in the following tables:

Patch No.	Allergen	Appearance	Allergen Identity
15	Carba Mix	Transparent, colorless or almost colorless patch	Pass identification of carba mix per Test Method 04786
16	Black Rubber Mix	Transparent, yellowish brown patch	Pass identification of black rubber mix per Test Method 04775
17	Negative Control	Transparent, colorless patch	
19	Mercaptobenzothiazole	Transparent, colorless or almost colorless patch	Pass identification of mercaptobenzothiazole per Test Method 04773
22	Mercapto Mix	Transparent, colorless or almost colorless patch	Pass identification of mercapto mix per Test Method 04774
24	Thiuram Mix	Transparent, colorless or almost colorless patch	Pass identification of thiuram mix per Test Method 03945

Test/Characteristic	Release Limits	Test Method
Assay of carba mix labeled amount: 0.25 mg/cm <sup>2</sup>	(b) (4)	04786
Assay of black rubber mix labeled amount: 0.075 mg/cm <sup>2</sup>	(b) (4)	04775
Assay of mercaptobenzothiazole labeled amount: 0.075 mg/cm <sup>2</sup>	(b) (4)	04773
Assay of mercapto mix labeled amount: 0.075 mg/cm <sup>2</sup>	(b) (4)	04774
Assay of thiuram mix labeled amount: 0.025 mg/cm <sup>2</sup>	(b) (4)	03945
Content uniformity	(b) (4)	(b) (4)
Content Uniformity continued	(b) (4)	(b) (4)
Microbial total count	Maximum of (b) (4) microorg/test	03672
Absence of (b) (4)	Pass	05094

Test/Characteristic	Release Limits	Test Method
Absence of (b) (4)	Pass	05095

### ***Analytical Testing of the Final Product and Method Validation***

The test methods and analytical methods validation are provided for the five allergens that constitute the Rubber Panel. These methods are the same as used for the licensed TRUE Test and are not reviewed by DMPQ, being under the purview of the product office.

### ***Microbiological Test Methods***

The Microbial Total Count of Patches Test Method (Method No: 03672-13 Dated Oct 2003) is provided in the submitted materials.

#### Method summary:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Methods for testing for the presence of for (b) (4) and (b) (4) in the currently licensed TRUE Test product is also provided in the submission.

### ***Validation of the Assembling Automation***

Automated equipment is used to (b) (4). The equipment is also used to (b) (4). This is the same equipment used in manufacture of the current TRUE Test and has been previously reviewed.

The validation document provided is a summary report for the assembly of the original TRUE Test panels 1 and 2. Testing was performed for the patch (b) (4)

All acceptance criteria were met in the execution of the study over the course of (b) (4) of manufacturing.

### **Equipment**

No new equipment is proposed in the submitted materials for the proposed new Rubber Panel. Equipment used for production is dedicated to a single allergen and labeled with the allergen number. I have the same opinion as previously stated in the Kearns review for STN 103738/5074, this submission raises no new issue with regard to the facility and equipment provided the firm responds to the Complete Response Deficiencies by stating no changes to the facility or equipment have been made since the submission of material for the Rubber Panel.

### **Equipment Cleaning**

Cleaning of equipment is described in SOP 052 *Cleaning of Rooms for Preparation and Packing of T.R.U.E. Test and Equipment in these Rooms* that is provided in the submitted material for the Rubber Panel. This SOP is the same version that was reviewed and found acceptable by Kearns in his review of STN 103738/5074.

(b) (4) water and (b) (4) water are used for cleaning. For equipment in contact with the (b) (4) the cleaning with water is (b) (4).

### **Microbial Cleaning Validation**

This provided cleaning validation is the same protocol reviewed by Kearns in STN 103738/5074. Kearns found the validation and results acceptable.

### **Computer Systems**

The firm states in the submitted material that all material transactions, stock data and approval procedures are documented manually on cards and in the batch documentation. The system is completely traceable.

### **Facility Description and Controls**

#### **Facility Layout**

A site plan is provided that highlights office areas, laboratory area, and the TRUE TEST manufacturing area. The facility depicted is the same as the area used to manufacture the currently licensed TRUE Test. Refer to Complete Response Letter Deficiency #1 and #2 on page 1 of this memo.

#### **Water Systems**

There is a (b) (4) water system for the facility that has previously been reviewed by DMPQ (Kearns STN 103738/5074). The firm states in the submitted materials for the water

system that it is unchanged since 2000. (b) (4) water monitoring is maintained and documented in SOP 044 and is analyzed (b) (4).

(b) (4) water and (b) (4) water are used for cleaning. For equipment in contact with the (b) (4) the cleaning with water is (b) (4).

Purchased (b) (4) water is used in product manufacture. Complete Response Deficiency #5 on page 2 of this review requests the firm to confirm that this procedure is still followed in product manufacture.

### **HVAC System**

Rudimentary drawing shows HVAC for TRUE TEST manufacturing areas Room (b) (4). HVAC was assessed by Kearns in STN 103738/5074 and found acceptable. The material presented in this submission is the same material presented to Kearns. Complete Response Letter Deficiency comments starting on page 1 of this review request the firm to provide any changes made to the facility since the original submittal of this material.

### **Environmental Monitoring**

SOPs provided in the submitted materials have been previously reviewed by Kearns and so only a summary will be provided.

#### ***SOP 082 Monitoring of Particles in Special Areas in Zone (b) (4)***

This SOP is from 2002 and describes the monitoring performed in the class (b) (4) in special areas of zone (b) (4). Zone (b) (4) is the area where production of the TRUE Test occurs. The SOP claims the production environment is class (b) (4) at rest. Particulate measurements are taken (b) (4) while the room is in a dynamic state. If no activity is planned on the day of monitoring, a static reading is taken.

Alert limits for particulate monitoring in this area are provided in the following table:

<b>Alert Limit</b>	<b>No. of particles (b) (4)</b>	<b>No. of particles (b) (4)</b>
Alert 1	(b) (4)	(b) (4)
Alert 2	(b) (4)	(b) (4)

#### ***SOP 926 Microbial Environmental Monitoring of TRUE TEST Premises***

This SOP is from 2003 and lists the sampling methods of viable air, settling plates, and contact plates or swabs for microbial environmental monitoring in the production areas.

Room monitoring activities are performed (b) (4), and personnel are sampled (b) (4) times per (b) (4).

Slit-sampling (b) (4)	Sedimentation (b) (4)	Surfaces (b) (4)	Type of Limit
(b) (4)	(b) (4)	(b) (4)	Alarm Limit
(b) (4)	(b) (4)	(b) (4)	Action Limit

\*) Alarm limit is (b) (4)  
. Action limit is (b) (4)  
.

Testing of gloves and clothes is performed for personnel monitoring - Acceptance criterion for this test is the absence of (b) (4). In case (b) (4) is detected, the head of the department is informed. The head of the production area shall prepare a deviation report.

A sampling map and results forms are included at the end of the SOP provided.

### **Container Closure**

The container closure for the proposed Rubber Panel is the same as the currently licensed TRUE Test. Components of the closure will only be summarized in this section since review has been previously performed.

### **Components of the closure and a listing of tests performed for each component:**

**Desiccant paper** Microbiological specification total count maximum (b) (4) microorganisms per test, additional tests – (b) (4)

**Packaging laminate** (b) (4) Tests – (b) (4)

**Sheet of** (b) (4) Tests - Microbiological specification total count maximum (b) (4) microorganisms per test, (b) (4)

(b) (4) Tests - Microbiological specification total count maximum (b) (4) microorganisms per (b) (4)

**Self-adhesive tape** (b) (4) Tests - Microbiological specification total count maximum (b) (4) microorganisms per (b) (4)

### **Prevention of Cross-Contamination and Product Mix-Up**

In order to prevent cross contamination when producing drug substance, only one allergen is manufactured (b) (4). All equipment used is dedicated to one allergen and labeled with the allergen number. There is (b) (4). The barcode on the package insert and the carton is read just before the final packing. Line clearance is performed between batches. Printed materials are stored under lock. Only the person handling the printed materials and the head of the production department has the key.

### **Stability**

The Final Report for Stability study of TRUE TEST Rubber Panel is provided in the submitted material – The report is actually a summary of Panel 2 of the original TRUE Test executed in 2005.

A stability study of 3 batches of T.R. U.E. Test panel 2 stored at 25°C/(b) (4) RH and (b) (4) has been performed. The study covers chemical tests and concentrations for each allergen, visual inspection of the allergen patches, and visual inspection of the package during storage at 25°C/(b) (4) RH for 24 months and storage at (b) (4). T.R.U.E. Test panel 2 contains 12 patches which are covered with individual allergen films, including the Carba mix, Black rubber mix, Mercaptobenzothiazole, Mercapto mix and Thiuram mix allergens in the current proposed TRUE Test Rubber Panel.

The examined T.R.U.E. Test panel 2 has the following configuration. The five allergens of current interest are highlighted in bold writing:

Patch No. Allergen:

13 p-tert-Butylphenol formaldehyde

14 Epoxy resin

**15 Carba mix**

**16 Black rubber mix**

17 Cl+ Me- Isothiazolinone (Kathon CG)

18 Quaternium 15

**19 Mercapto benzotltiazole**

20 p-Phenylenediamine

21 Formaldehyde

**22 Mercapto mix**

23 Thiomersal

**24 Thiuram mix**

The stability protocol for this product assesses assay of the allergen substance, visual inspection of the patches, and visual inspection for appearance of the package. The firm reports that acceptable values were obtained for the five allergens after storage at 25°C/(b) (4) RH after 24 months of storage.

The firm's intention for the proposed Rubber Panel is storage at 25°C/(b) (4) RH.

### ***Stability Commitment from Firm***

The first 3 commercial batches will be tested according to the stability testing plan. A microbiological assay for total count and absence of (b) (4) is included in the proposed stability plan.

### **Review History**

Date Prepared: RHC 19 December 2014

Date Commented:

Date Revised: RHC

Date Final: RHC