

**From:** Houck, Christina M  
**Sent:** Friday, December 11, 2015 3:32 PM  
**To:** Kim Sullivan (sullivan@smarthealth.com)  
**Cc:** Valenti, Elizabeth  
**Subject:** STN 125579 IR

Dear Kim,

We are reviewing your BLA for STN 125579/0 for Rubber Panel T.R.U.E. TEST (Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test) for “use as an aid in the diagnosis of allergic contact dermatitis in persons six years of age and older whose history suggests sensitivity to one or more of the five substances included on the Rubber Panel T.R.U.E. TEST.” After further review we have the following information request:

1. Please provide occupational and/or environmental histories to rubber allergens for each participant enrolled in the 6 studies proposed to be included in the label (5 adult studies and 1 pediatric study).
2. Please complete the following 4 tables to show data from the adults studies (Studies 1-5) on the safety and diagnostic performance of the Rubber Panel T.R.U.E. TEST for adults aged 18 through 64 years of age and adults aged  $\geq 65$  years of age.

<b>Clinical Study Overview</b>	Study	Study	Study	Study	Study 5	Total
N	127	121	119	50	49	466
<i>Age Range (years)</i>	<i>19-79</i>	<i>18-77</i>	<i>19-76</i>	<i>19-82</i>	<i>18-68</i>	<i>18-</i>
18-64 y (n)						
Female (n)						
≥65 y (n)						
Female (n)						

**Incidence and Proportion of Poor Panel Adhesion**

	Study	Study	Study	Study	Study	Total
N	127	121	119	50	49	466
Poor Adhesion	0	14	2	5	12	33
18-64 y (n)	0					
≥65 y (n)	0					

**Total Adverse Events in Adults** (modified from your IR response)

	General Panel	Black Rubber Mix	MBT	Mercapto mix	Thiuram mix
	N=345	N=290	N=290	N=290	N=345
Total Adverse Events in adults	<b>28</b>	<b>4</b>	<b>5</b>	<b>7</b>	<b>7</b>
≥65 y (n)					
Erythema (n)	—	<b>2</b>	<b>2</b>	<b>3</b>	<b>1</b>
≥65 y (n)	—				
Hyperpigmentation (n)	—	—	<b>2</b>	<b>3</b>	<b>2</b>
≥65 y (n)	—				
Pruritus (n)	<b>28</b>	<b>2</b>	<b>1</b>	<b>1</b>	<b>4</b>
≥65 y (n)					
<i>Combined Study Data (Studies 2,3,4,9 applicable)</i>					

**Available Frequency\* Estimate of Positive Reactions to the Rubber Panel T.R.U.E. TEST Allergens**

	Frequency	Study 127	Study 121	Study 119	Study 50	Study 49
<b>Carba mix</b> Position 15 (Studies 2, 3, and 4)	<b>6/290</b>					
18-64y (n)						
Female (n)						

≥65 y (n)						
Female (n)						
<b>Black rubber mix</b> Position 16 (Studies 2, 3, and 4)	<b>5/290</b>					
18-64y (n)						
Female (n)						
≥65 y (n)						
Female (n)						
<b>Mercapto mix</b> Position 22  (Studies 2, 3, and 4)	<b>9/290</b>					
18-64y (n)						
Female (n)						
≥65 y (n)						
Female (n)						
<b>Thiuram mix</b> Position 24 (Studies 1, 3, 4 and 5)	<b>14/345</b>					
18-64y (n)						
Female (n)						
≥65 y (n)						
Female (n)						
<b>Mercaptobenzothiazole</b> Position 32  (Studies 2, 3, and 4)	<b>8/290</b>					

18-64y (n)						
Female (n)						
≥65 y (n)						
Female (n)						

3. 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.
4. In your submission you provided a completion date of November 2015 for the gap analysis and your plan to address the quality system regulations related to the device component of your combination product. Please provide your completed gap analysis and project plan to address the following regulations:
  - § 820.20.- Management responsibility
  - § 820.30.-Design controls
  - § 820.50.-Purchasing controls
  - § 820.100.-Corrective and preventive action

The following requests are in response to the executed batch record:

5. Please provide a detailed description of the process of (b) (4) patches from the Rubber Panel (b) (4), the placement of the patches on the tape, and the pouch packaging of the test strip. Please include details, such as whether the individual Rubber Panel T.R.U.E. TEST allergen (b) (4) are (b) (4) independently or simultaneously, and whether test strips are assembled one at a time or in multiples.
6. On page 6 of the batch record it appears that (b) (4) specifications were not met when production started on January 5 and 6, 2015. The specification for (b) (4) is listed as (b) (4) and (b) (4) should be between (b) (4). The (b) (4) result is documented as (b) (4) and (b) (4) on January 5 and 6, 2015, and the (b) (4) values for both days are all at or (b) (4). Please clarify what affect these conditions had on the operations performed on these specific days, and if any deviations or corrective actions were associated with these events.

7. In the table on page 7 of the batch record, the (b) (4) test of the vision system is lined out and the test appears to not have been performed. Please describe how (b) (4) testing of the vision system is performed and indicate how acceptability of testing is documented.
  
8. On pages 24 and 25, the executed batch record appears to document reconciliation of used foil and calculation of yield. The written notes are barely legible; however, it appears a 97% deviation is noted for the pouches when the limit is specified as (b) (4). It also appears that of the (b) (4) pouches manufactured, (b) (4) of the pouches were rejected, (b) (4) were sampled, (b) (4) pouches were considered the yield, and the total number of pouches produced was below the specified mean. Please elaborate on the following items:
  - a. Please confirm a pouch at this step contains a test strip.
  
  - b. Please provide calculations regarding the deviation of the number of pouches manufactured and whether 'Double pouches – empty' are retained or discarded.
  
  - c. Please include any investigations performed assessing the documented low yield.

Kind Regards,

Christina

Christina Houck

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