

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Center for Biologics Evaluation and Research
Division of Bacterial, Parasitic, and Allergenic Products (DBPAP)

Date: June 9, 2006

From: Bo Chi, M.D., Ph.D., DBPAP

/s/

Subject: Review of STN103738/5031, for a new panel containing five rubber related allergen patches

To: Jennifer Ross, DVRPA

Mekos submitted the above-cited supplement to the T.R.U.E TEST BLA for 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.

Drug substance (Attachment 0, Page 1):

1. Carba Mix

Concentration: 0.25 mg/cm²
Allergen components: Diphenylguanidine, 0.067 mg
(per patch) Zincdibutyldithiocarbamate, 0.067 mg
Zincdiethyldithiocarbamate, 0.067 mg
Vehicle: Hydroxypropyl cellulose

2. Black Rubber Mix

Concentration: 0.075 mg/cm²
Allergen components: N-isopropyl-N'-phenyl paraphenylenediamine, 0.0102 mg
(per patch) N-Cyclohexyl-N'-phenyl paraphenylenediamine, 0.0255 mg
N,N'-diphenyl paraphenylene-diamine, 0.0255 mg
Vehicle: Polyvidone

3. Mercaptobenzothiazole

Concentration: 0.075 mg/cm²
Allergen component: Mercaptobenzothiazole, 0.061 mg
(per patch)
Vehicle: Polyvidone

4. Mercapto Mix

Concentration: 0.075 mg/cm²
Allergen component: N-cyclohexylbenzothiazyl-sulfenamide, 0.0203 mg
(per patch) Dibenzothiazyl disulfide, 0.0203 mg
Morpholinylmercaptobenzothiazole, 0.0203 mg
Vehicle: Polyvidone

5. Thiuram Mix

Concentration: 0.025 mg/cm²
Allergen component: Tetramethylthiuram monosulfide, 0.0051 mg
Tetramethylthiuram disulfide, 0.0051 mg
Disulfiram, USP, 0.0051 mg,
Dipentamethylenethiuram disulfide, 0.0051 mg
Vehicle: Polyvidone

Source material specifications are in accordance with in house monographs to include a qualitative test (b) (4), a quantitative test, and a microbiological test method (Attachment 11). The protocols and methods have been approved, therefore are not provided.

Content Uniformity:

(b) (4) content uniformity data of three validation batches of the previous panel, Panel 2.1, were presented and the results are acceptable (Attachment 17). Of the (b) (4) analysis for each allergen product, the (b) (4). Maximum (b) (4) values were outside the (b) (4) limit, none was outside the (b) (4) limit, and the RSD was (b) (4).

The sponsor proposed a new specification for future assessment of (b) (4) content uniformity data (Attachment 17). According to the new specification, (b) (4) analyses will be performed for each allergen product instead of the approved (b) (4) analysis. (b) (4) analysis will be (b) (4) (b) (4) values will be outside the (b) (4) limit, none will be outside the (b) (4) limit, and the RSD will be (b) (4). Based on a Poisson distribution, the 95% upper confidence limit for failure of the new specification is higher than that of the approved one and need to be revised.

A comment on the firm's proposed new specification is provided in the CR Letter Comments section of this memo for inclusion into the Complete Response (CR) letter.

Specifications:

(b) (4) assays serve as both the identity test and the quantitation test (Attachment 26).

The sponsor proposed a new analytical method 04774-05 for determining the content of Mercapto Mix in T.R.U.E test [Attachment 26, Page 6(22)]. The previous method 04774-04 had a problem with (b) (4). The validation changes include (b) (4)

(b) (4). The parameters validated include (b) (4); range, repeatability, intermediate precision, and stability of standard and sample solutions. The results are acceptable.

A comment on the firm's (b) (4) for black rubber mix and mercaptobenzothiazole is provided in the CR Letter Comments section of this memo for inclusion into the CR letter.

Product Stability (Attachment 18): The stability data of three lots of the previous T.R.U.E. Test, Panel 2, were presented. The results from chemical tests, visual inspection of package and allergen patches show that the stability of patches coated with carba mix, black rubber mix, mercaptobenzothiazole, mercapto mix and thiuram mix stored at 25°C (b) (4) RH are acceptable.

Therefore, the sponsor proposed this product to be stored at room temperature and the expiry to be 24 months (Page 8). However, these results are based on the previous T.R.U.E. Test, Panel 2, and not the assembled rubber panel product. Therefore stability data for the final assembled rubber panel product needs to be submitted.

A comment on the firm's proposed expiration date is provided in the CR Letter Comments section of this memo for inclusion into the CR letter.

CR Letter Comments

1. In Attachment 17, you proposed a new specification for future assessment of (b) (4) content uniformity data. In the current approved specification, (b) (4) analyses are performed, with (b) (4) failures (outside the (b) (4) limit but within the (b) (4) limit) permitted. According to the proposed specification, (b) (4) analyses will be performed for each allergen product, with (b) (4) failures permitted. Based on a Poisson distribution, the 95% upper confidence limit for (b) (4) failures is (b) (4) failures, or (b) (4) (b) (4) . However, the 95% upper confidence limit for (b) (4) failures is (b) (4) , or (b) (4) (b) (4) . Please revise the new specification to make the 95% upper confidence limit for failure in the proposed specification consistent with the existing one.
2. Expiration dating will be based upon real-time stability data of the final assembled product in the proposed configuration. Please provide stability data for the final assembled rubber panel product.
3. Please provide a lot release protocol for the new rubber panel. In addition, you will need to submit samples of the first production lot along with analytical standard raw materials to CBER for CBER lot release testing. Please acknowledge.
4. In attachment 20, "determination of black rubber mix in T.R.U.E.TEST", appendix 1, the (b) (4) of black rubber mix sample has (b) (4) . Likewise, in the same attachment in "determination of mercaptobenzothiazole in T.R.U.E. TEST", appendix 1, the (b) (4) of mercaptobenzothiazole sample has (b) (4) . Please explain.
5. In attachment 20, at the bottom of page 2(8), the unit of concentration of black rubber mix standard (b) (4) should be (b) (4) instead of μg . Likewise, on page 2(7), the unit of concentration of thiuram mix standard (b) (4) should be (b) (4) instead of μg . Please correct.
6. We reserve comment on the proposed labeling until the supplement is otherwise acceptable.