Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

**To:** **STN 125478 Short Ragweed Pollen Allergen Extract**

**From:** Deborah Trout, BLA Committee Member, OCBQ/ DMPQ/MRB1 HFM-675

**Through:** Carolyn Renshaw, Branch Chief, MRB1, DMPQ, OCBQ, HFM-675

**Subject:** Review of BLA-amendment 125478/0.22 to request for additional information regarding a deviation to a critical process parameter noted at the DP manufacturer.

**Action Due:** April 17, 2014

**Recommended Action:** *The investigation conclusion and corrective actions associated with this deviation appear adequate. Future manufacturing of Ragwitek® will use the* (b) (4) *filed in BLA 125478.0. I reviewed stability data for water content* (b) (4) *disintegration time (modified* (b) (4) *and microbial enumeration* (b) (4) *All results met the acceptance criteria. I defer evaluation of all other analysis of stability batches to the product reviewer*

**Review Narrative:**
In the cover letter of the March 3, 2014 amendment (0.19), Merck indicated that a deviation to a critical process parameter (CPP) in drug product lots manufactured at Catalent intended to support commercial launch was observed during a recent review of the continued process verification report. Merck committed to inform the FDA of the conclusion of this investigation upon its completion by March 10, 2014.

The investigation of this deviation relates to (b) (4) During a root cause investigation, (b) (4) was found to be incorrect in the Master Batch Record created for the commercial manufacture of Ragwitek®. The DP manufacturer used the Grastek® (b) (4) of Ragwitek® lots. In following SOP 47/255 for the preparation of Master Batch Records, Catalent based the commercial Ragwitek® batch records on those of Grastek®, as the starting template.

The requirement for changing the (b) (4) with respect to Grastek® (b) (4) for Grastek® (b) (4) for Ragwitek®) was not captured in the change control for the creation of the

Ragwitek® Master Batch Record. CAPAs have been applied to develop a more robust process for Batch Record creation and approval. SOP 47/255 will be updated to include the requirement for a full list of Critical Process Parameters (CPPs) to be attached to all change controls for the creation of new revisions of Master Batch Records, and documented verification by both Catalent and the client. The incorrect Master Batch Record has been made obsolete. Future manufacturing of Ragwitek® will use the filed (b) (4) filed in BLA 125478.0.

An investigation concluded there is no Ragwitek® product impact due to the manufacture at a (b) (4). Data indicate all the (b) (4) commercial Ragwitek® batches manufactured to date passed all the in-process checks during (b) (4)

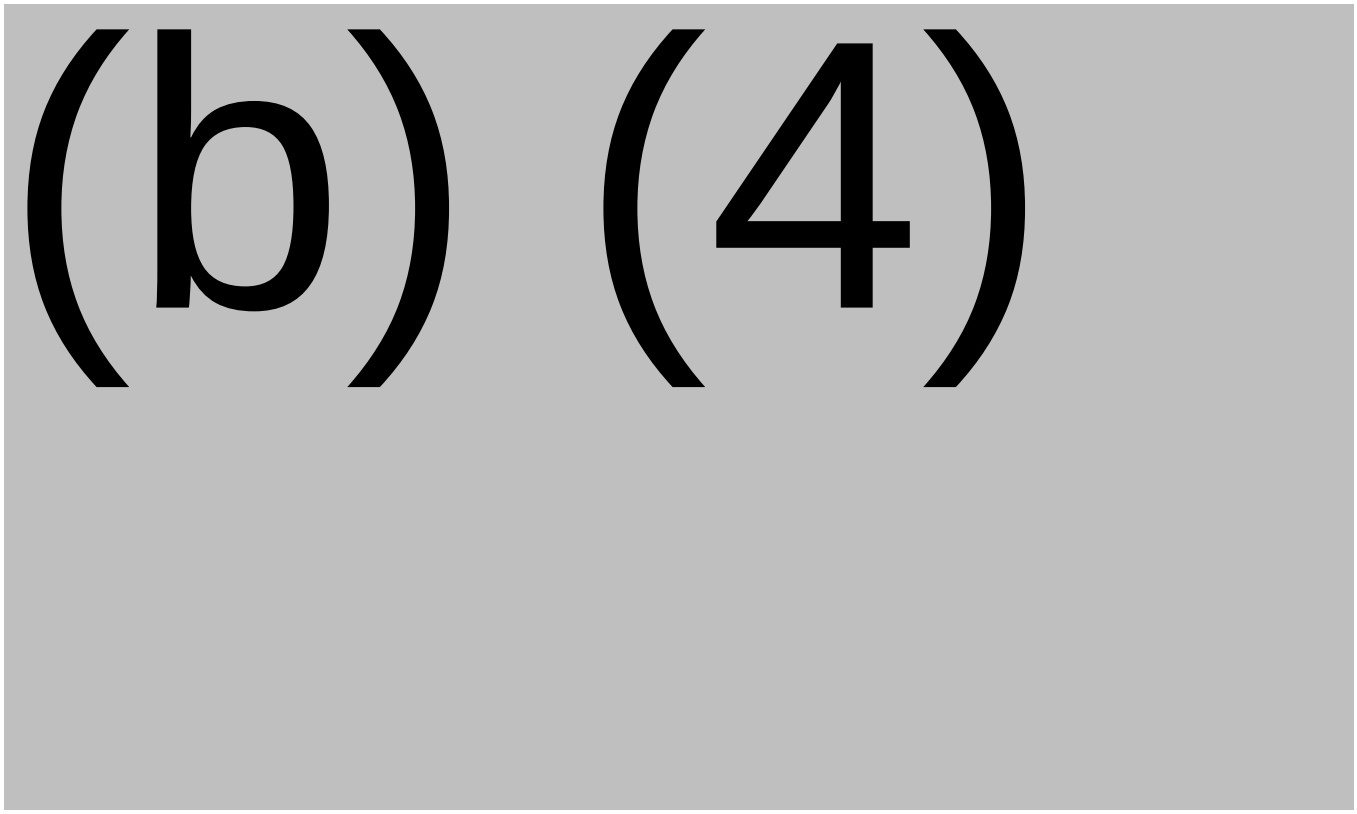
A shipping study that simulated shipment of product by air, sea and ground was satisfactorily performed on Grastek® bulk packaging (b) (4).

Grastek® and Ragwitek® are similar in that they share the same base formulation and method of Drug Product manufacture. In particular, the (b) (4) (Catalent, Swindon, UK) and identical packaging components are used. Therefore correlations in stability data and packaging studies can be applied. The registration stability batches of Ragwitek® were (b) (4) as the commercial batches. Data from these registration stability batches at (b) (4) and at (b) (4) are all complete and satisfactory. In addition, stability data from the (b) (4) Grastek® Drug Product PPQ lots manufactured with (b) (4) on (b) (4) have been completed at (b) (4)

*I reviewed stability data for water content* (b) (4) *disintegration time (modified* (b) (4) *and microbial enumeration* (b) (4) *All results met the acceptance criteria. I defer evaluation of all other analysis of stability batches to the product reviewer.*

The initial intention was for Ragwitek® (b) (4) to reflect the same (b) (4) as for Grastet® given that the two products use the same pack materials and (b) (4). In line with this intention, the Ragwitek" (b) (4) registration stability batches were manufactured using the (b) (4)

Study PR336917R was conducted to assess a range of (b) (4) on (b) (4) All data presented in this report were generated during the development of another product which utilized identical pack materials and tooling to those used for Grastek® and Ragwitek®. The (b) (4) was the primary in-process test to determine acceptable (b) (4). In addition, (b) (4) were evaluated by a panel. At all conditions the (b) (4) test passed, however there were some (b) (4)




The study concluded that, although the seal integrity was acceptable across the window of (b) (4) with a set point of (b) (4)

The (b) (4) in-process checks for determination of (b) (4) are the (b) (4) (b) (4) are subjected to the (b) (4) A further (b) (4) units per batch are used in a final QA inspection. The total number of units tested per batch is given in Table 5.

(b) (4)

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