Our STN: BL 125713 **COMPLETE RESPONSE**

DBV Technologies S.A. August 3, 2020
Attention: Pharis Mohideen, M.D.
25 Deforest Avenue
Summit, NJ 07901

Dear Dr. Mohideen:

Please refer to your Biologics License Application (BLA) submitted and received on August 6, 2019, for Peanut (*Arachis hypogaea*) Allergen Extract manufactured at your (b) (4) location and submitted under section 351(a) of the Public Health Service Act.

We have completed our review of all the submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

CLINICAL

1. Study V712-301 failed to meet pre-specified success criteria both for the primary efficacy endpoint (lower bound of the 95% confidence interval around the efficacy estimate was 12.4%, compared with success criterion ≥15%) and for the adhesion sub-study (failure rates of 38.7% and 18.7% for DBV712 systems and placebo systems, respectively, compared with success criterion <10%). The clinical data submitted to your BLA do not support a definitive conclusion that efficacy is not adversely affected by adhesion failure, and data are insufficient to adequately assess reasons for adhesion failure to allow for mitigation measures (e.g., reason for detachment was reported as "unknown" for 43.1% of DBV712 system failures and 60.1% of placebo system failures). As these unacceptably high rates of adhesion failure occurred under conditions of a clinical trial, we are concerned that adhesion failures, and potential adverse impact on effectiveness, will be even greater in the context of real-world use where measures to ensure adhesion (including but not limited to patient/parent education and follow-up) will not be feasible to implement to the same extent as in a clinical trial. Furthermore, clinical data suggest that adhesion failure due to mechanical disruption (scratching) may occur most often in patients who are most peanut-sensitive and therefore most likely to experience itching at the application site. Consequently, we are concerned that in addition to failing to meet the primary efficacy endpoint success criterion, the results of study V712-301 may substantially overestimate real-world effectiveness of the DBV712 epicutaneous system, particularly in highly peanut-sensitive patients at highest risk for serious allergic reactions. In summary, we are unable to conclude that the DBV712 epicutaneous system is

safe and effective with favorable benefit/risk for its intended use in patients with IgE-mediated peanut allergy.

2. To address the deficiencies outlined above, you will need to: reformulate your final drug product to improve adhesion of the product, demonstrate adequate *in vivo* adhesion performance of the re-designed product for the proposed duration of wear, and demonstrate safety and effectiveness of the re-designed product in one or more adequate and well-controlled clinical trials.

   a. To improve adhesion of your product, we recommend you consider the use of different adhesive components (i.e., the (b) (4)) and that you consider modification of the (b) (4) of each adhesive component. In addition, since (b) (4) of epicutaneous systems in the per protocol adhesion set were graded with an adhesion score of (b) (4) at the time of application, you may consider improvement in overall product design to facilitate proper application (such that the product is fully adhered at the time of application).

   b. The most straightforward approach to demonstrating effectiveness of the re-designed product would be to conduct a placebo-controlled efficacy trial, similar to study V712-301. You may consider incorporating certain study design elements to better inform factors affecting benefit-risk considerations for use of this product. These design elements might include: exploration of various durations of wear (to determine the minimum duration of wear necessary for the product to be effective), analyses of efficacy outcomes in age and screening ED subgroups (serving to inform specific populations in which this product may be more effective), inclusion of post-treatment challenge doses between the (b) (4) and (b) (4) range (e.g.,(b) (4) , to provide another quantitative estimate for tolerance of accidental exposure), and evaluation of the optimal time of day for application and subsequent removal based on prescribed duration of wear (to reduce cases of provoked patch detachment, e.g., scratching of the skin due to itching, water exposure, exercise, or other factors).

   c. We would be willing to consider a proposal for other types of studies, in lieu of a placebo-controlled efficacy trial, to demonstrate effectiveness of the re-designed product. You could include in your proposal an approach to leverage the observed efficacy in Study V712-301, provided that the approach is justified by a solid scientific rationale and data. Please note that your study(ies) will need to adequately demonstrate safety of the re-designed product regardless of the approach to demonstrate effectiveness.

   d. The study to assess *in vivo* adhesion may be an independent/dedicated study or may be incorporated into an efficacy trial or other type of study to demonstrate safety and/or effectiveness, as discussed above. Specific elements of study design, including thresholds for demonstrating acceptable adhesion, will require further discussion prior to conduct of the study. At a minimum, the study should assess adhesion at equally spaced timepoints

(e.g., every 4 or 6 hours) from the time of application to obtain an estimate of the average time to any level of adhesion failure (i.e., adhesion score of 2 or 3). Ultimately, the impact of adhesion performance on effectiveness and safety will be considered as part of the benefit-risk framework in our review of a licensure application for a re-designed product.

Human Factors Consult review deficiencies identified:

3. Based on the submitted human factors (HF) study results, including the root cause analysis, study participants' subjective feedback, and your analysis of the results, we have determined that the product user interface does not support safe and effective use. We remain concerned about use errors and task failures resulting in the risk of systemic allergic reaction if allergen comes in contact with (b) (4) . We note that the study results, root cause analysis and participants' subjective feedback pointed to multiple aspects of the user interface that could be further optimized as it pertains to all critical tasks involving (b) (4)

   Therefore, we recommend you implement additional mitigations, based on a re-evaluation of the HF study results, root causes, and participants' subjective feedback, to further optimize the product user interface (which includes the patch, pouch label, carton labeling, and instructions for use (IFU)) to promote the safe and effective use of the proposed product. Furthermore, we note that important information related to the proper use of the product is not included in the currently proposed IFU. For example, instructions on what the user should do regarding swimming, bathing, and heat sources are not provided and thus, such critical knowledge tasks were not evaluated in the current HF study. Therefore, this aspect of the user interface should also be further optimized to promote the safe and effective use of this product.

   Once you implement additional mitigations to address our concerns and any other mitigations that you determine necessary, and after addressing the other deficiencies outlined in this letter that may impact your user interface, we recommend that you finalize your to-be-marketed product user interface and conduct a HF validation study that demonstrates that your revised user interface: a) can support safe and effective use for the intended users, uses, and use environments; and b) does not introduce different risks.

   Additionally, we strongly recommend you submit your study protocol for feedback from the Agency before commencing your study. We strive to review and provide comments on the HF validation study protocol within 60 days, as resources permit. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company. Please refer to our draft guidance titled Contents of a Complete

Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/contents-complete-submission-threshold-analyses-and-human-factors-submissions-drug-and-biologic) for the content of a human factors validation study protocol submission.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4– Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents:

Applying Human Factors and Usability Engineering to Medical Devices, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-product-design-minimize-medication-errors-guidance-industry

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-factors-studies-and-related-clinical-study-considerations-combination-product-design-and

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/contents-complete-submission-threshold-analyses-and-human-factors-submissions-drug-and-biologic

CHEMISTRY, MANUFACTURING, and CONTROLS:

(b) (4)

(b) (4)

(b) (4)

3.2.S.2.3 Control of Materials – (b) (4)

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

3.2.S.2.4 Controls of Critical Steps and Intermediates

(b) (4)

3.2.S.2.5 Process validation and/or evaluation

(b) (4)

(b) (4)

3.2.S.2.6 Manufacturing development

(b) (4)

(b) (4)

3.2.S.3 Characterization

(b) (4)

3.2.S.4.2 Analytical procedures

(b) (4)

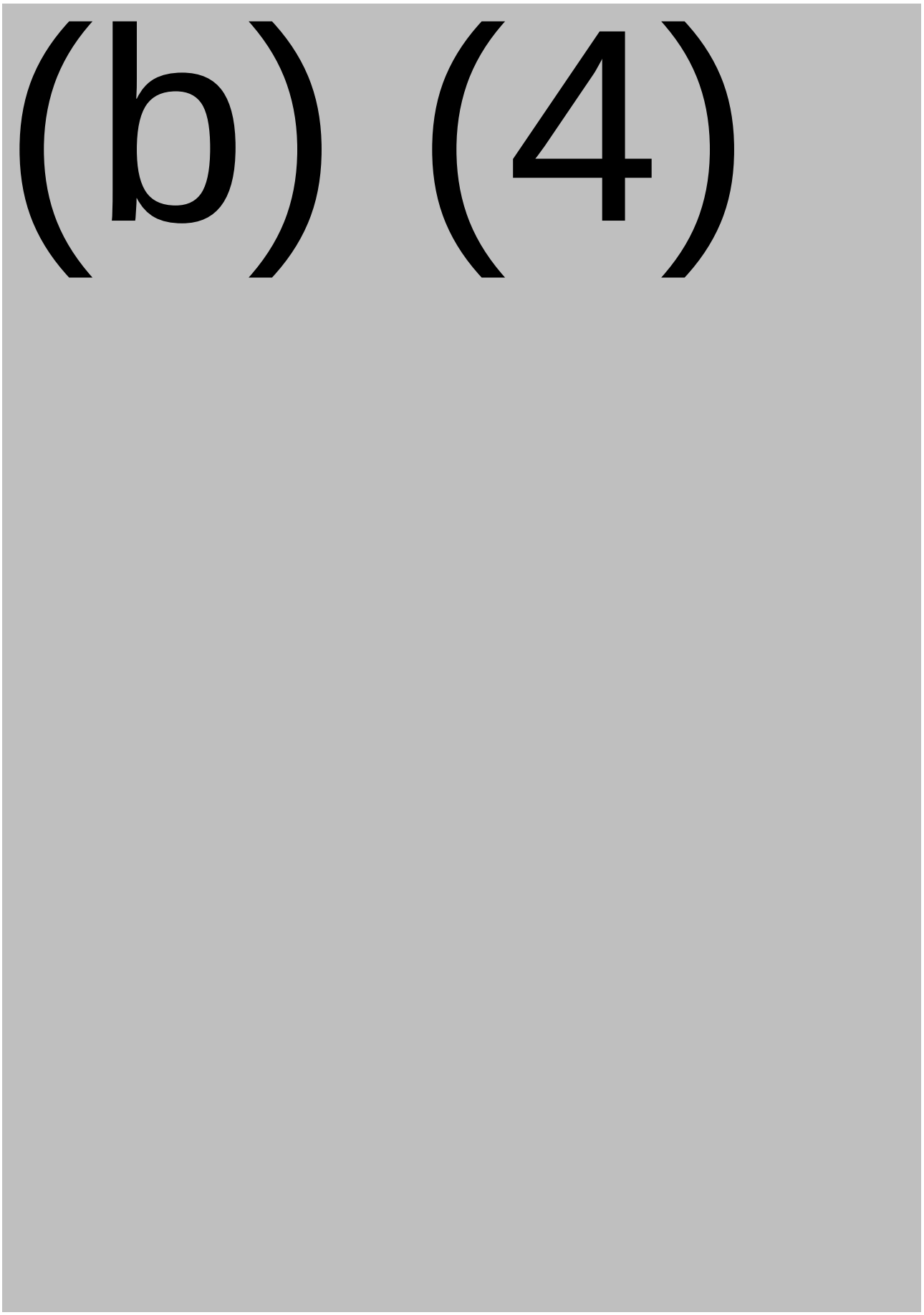
(b) (4)

3.2.S.4.3 Validation of analytical procedures

(b) (4)

(b) (4)

(b) (4)


(b) (4)

(b) (4)

3.2.S.4.5 Justification of specification

(b) (4)

(b) (4)

3.2.S.5 Reference Standards

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.S.7 Stability

(b) (4)

Non-Clinical Statistical deficiencies identified:

(b) (4)

(b) (4)

(b) (4)

3.2.P.4 - Components

(b) (4)

3.2.P.5 – Control of Drug Product

(b) (4)

(b) (4)

MANUFACTURING AND PRODUCT QUALITY

(b) (4)

(b) (4)

LABELING

80. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider

your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

Please submit your meeting request as described in CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm, or may be requested from the (b) (4) .

If you have any questions regarding the above, please contact the (b) (4)

Sincerely,

(b) (4)

Center for Biologics Evaluation and Research

(b) (4)

Center for Biologics Evaluation and Research