CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761192Orig1s000

OTHER ACTION LETTERS

BLA 761192

COMPLETE RESPONSE

MediWound, Ltd.
c/o Vericel Corporation
Attention: Michael Halpin
Chief Operating Officer
64 Sidney Street
Cambridge, MA 02139

Dear Mr. Halpin:

Please refer to your biologics license application (BLA) dated and received June 29, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for "concentrate of proteolytic enzymes enriched in bromelain" gel.

We also acknowledge receipt of your amendments dated April 16, 23, 30, and May 28, 2021 which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Botanical Raw Material

1. Botanical raw material (BRM) authentication is solely based on morphology. BRM authentication should include genetic, chemical, or biological methods with appropriate acceptance criteria. We acknowledge your response to the information request (IR) dated January 25, 2021, where you proposed to include biological and chemical assays as additional authentication methods. However, at this time, this continues to be a deficiency.

Bromelain Special Production (BSP) and Drug Substance (DS) Microbiology

2. The overall microbial control strategy does not mitigate the risk of potential adventitious agents that may be introduced during the manufacturing process. The current BSP and DS manufacturing processes do not have adequate microbial control for in-process intermediates. Implement a microbial control

strategy in accordance to USP <61> (bioburden monitoring) and/or USP <51> (antimicrobial effectiveness testing) that mitigate potential adventitious agents that may be introduced during the manufacturing process and provide microbial limits for all BSP in-process intermediates. Provide microbial method validation data for in-process samples in 3.2.S.2.5.

3. Due to the nature of BSP and DS, routine endotoxin testing cannot be performed (b) (4)

4. (b) (4)

5. (b) (4)

6.

7. Microbial limits for the BSP intermediate bulk have not been provided in 3.2.S.2.4, therefore it is not possible to evaluate the microbial quality during the BSP manufacturing process. Implement microbial limits of the in-process samples to demonstrate adequate microbial control during the BSP manufacturing process.

8. The BSP microbial limit for release in 3.2.S.2.4 does not demonstrate adequate microbial control and poses substantial risk to product quality during routine shipping conditions. [redacted] to mitigate the risk of potential adventitious agents and to demonstrate microbial control during shipping.

9. The microbial limits for the DS manufacturing processes in 3.2.S.2.4 do not adequately reflect microbial quality of the in-process bulk [redacted] Provide bioburden limits of the in-process bulk DS [redacted]

10. We acknowledge the endotoxin test method qualification data for the [redacted] that was provided on January 25, 2021 and your proposal to [redacted] However, at this time, this continues to be a deficiency.

11. The method suitability for bioburden release testing for DS did not meet acceptance criteria for [redacted]. Repeat the bioburden test method suitability for burden testing of the DS.

12. Facility information for the manufacturing site Challenge Bioproducts Company Ltd (FEI 3004282026) has not been provided. Provide the establishment information in Module 3.2.A.1 for all manufacturing facilities proposed in your submission.

Drug Product - Microbiology

13. Report RP-V-P-0163 for container closure integrity test (CCIT) validation does not meet the acceptance criteria to detect 20 micron leaks. Revised validation study data should be provided to demonstrate that the test equipment and methodology can successfully detect all breaches ≤ 20 micron.

14 [redacted]

15 [redacted]

16. Method validation for in-process bioburden testing to meet the detection limit and acceptance criterion of ≤10 cfu/10 mL (total [(b) (4)] for the gel vehicle carbomer [(b) (4)] is not provided in the IR response of January 25, 2021. Provide this information.

17. Clarify if [(b) (4)] are also monitored as part of in-process controls for the NexoBrid drug product and gel vehicle proposed in 3.2.P.3.4 and provide the acceptance criteria.

18. Regarding BI D-values in the gel vehicle, D-value in the gel-vehicle product validation data or information is not provided in your IR response of January 25, 2021. Provide this information.

19. Regarding in-process bioburden method qualification (IR#6 and #19), method qualification data is not provided in your IR responses of January 25, 2021. Provide this information.

Product Quality - Chemistry, Manufacturing, and Controls (CMC)

20. In your January 25, 2021 response to the IR sent on December 21, 2020, you commit to provide the following data:
    a. Data results of BSP, DS, and DP process validation executed according to the protocols submitted with your January 25, 2021 response
    b. [(b) (4)] study and a toxicological assessment
    c. Extractable study on the DP and GV rubber stoppers
    d. Elemental analysis by ICP-MS on the DP and the gel vehicle (GV) in their final container closure system
    e. In-use stability study performed on batches manufactured using the proposed commercial manufacturing process

    To date, these continue to be deficiencies. Provide these items to support your application.

21. We recommend that you include an assessment of all critical and non-critical in-process controls and operational control parameters as outlined in the February 17, 2021 CMC amendment (Section 3.2.S.2.4) to your re-validation protocols. Additionally, provide the results for all critical parameters assessed during process re-validation in section 3.2.S.2.5.

22. The BLA indicates that the container closure system for BSP is an [(b) (4)] [(b) (4)]. Provide information on the manufacturer and composition of the [(b) (4)], its potential extractables/leachables, and an assessment of potential risks to product quality.

23. Regarding your stability studies for BSP,
    a. It is unclear how sampling for BSP stability testing is performed. Clarify the sampling procedure for BSP stability testing.
    b. Describe the container closure system used to store BSP for stability studies and how it is representative of the proposed commercial container closure system for BSP.
    c. It is not clear which methods are being used to test the samples for the BSP stability study. For each method, provide the method codes and indicate the level of qualification or validation that has been performed.
    d. There are no post-approval stability protocols for BSP. Annual stability studies are helpful in identifying unexpected changes in product quality throughout the product life-cycle. Considering the potential batch-to-batch variability of the botanical raw materials, we recommend that you continue to monitor the stability of at least one BSP batch a year post-approval. Provide a BSP post-approval stability protocol to the BLA.
    e. Except for the registration batches and batch BSP-02-15, all other batches in the stability study were manufactured between 2008-2011. Provide additional stability data, if available, for BSP batches used to manufacture the pivotal clinical drug product batches.

24. (b) (4) Describe if and how this process is conducted and describe the control strategies in place to prevent contamination and minimize BSP degradation.

25. Report QC-0087 describes the validation of the RP-HPLC method TP-0085. Regarding the validation of TP-0085,
    a. The validation report indicates that an external commercially sourced reference standard is used that has good stability and reliability at resolving peaks. Provide additional details on the external standard used, including the source and quality specifications.
    b. The validation report indicates that different analysts were involved to validate intermediate precision. However, based on Tables 14-17 of validation report QC-0087, only analyst A performed the test. Confirm whether multiple analysts were involved in the validation of intermediate precision.

26. Report QC-0026 and QC-0057 describes the validation of the (b) (4) method TP-0001. Regarding the validation of TP-0001,
    a. The (b) (4) is a critical reagent for this assay. Provide data supporting the robustness of the assay against variability in the (b) (4) (b) (4)
    b. Provide SOP-TP-0001 which should include details on system suitability tests used for this method.

c. Provide a description of how new batches of [redacted], as a critical reagent, are qualified for use.

27. Report MW-R-4562 describes the feasibility study of the [redacted] and [redacted] detection method 11-006. This study only provides evidence for the absence of factors in BSP that could interfere with the performance of the [redacted] method. Provide the method validation reports supporting the sensitivity, selectivity, and robustness of this method to detect [redacted] and [redacted] in BSP.

28. Report T-02 describes the validation of the [redacted] method TP-0002. Regarding the validation of TP-0002,
    a. The [redacted] is a critical reagent for this assay. Provide data supporting the robustness of the assay against variability in this reagent.
    b. Provide SOP-TP-0002 which should include details on system suitability tests used for this method.
    c. Provide a description of how new batches of [redacted], as a critical reagent, are qualified for use.

29. Report QC-0063 describes the validation of the [redacted] method TP-0049.
    Regarding the validation of TP-0049,
    a. The report claims that robustness was demonstrated in the framework of method development; however, the information was not provided. Provide data supporting the robustness of the method against perturbations in assay parameters.
    b. Additionally, considering that [redacted] is a critical reagent for this assay, provide data supporting robustness against variability in [redacted]
    c. Provide SOP-TP-0049 which should include details on system suitability tests used for this method.
    d. Provide a description of how new batches of [redacted] as a critical reagent, are qualified for use.

30. You propose to test the NexoBrid Drug Product and Gel Vehicle mixture at release using tests for appearance, pH, homogeneity, and viscosity. However, the mixture is not tested for potency. Provide justification for not including a test(s) for potency as part of the release of the mixture.

31. We acknowledge that you are proposing to use the USP <561> for pesticide residue testing; however, the acceptance criteria for release of drug product is defined as “limits as per USP.” This acceptance criterion does not allow for a lot-to-lot comparison. We recommend that the pesticide residue results are also reported as absolute values as part of the specification.

32. Section S.3.1 <Elucidation of Structure and Other Characteristics> includes data on the composition of NexoBrid DP such as the identities and relative quantities of the [redacted] and their degradation products. However, the section does not include data connecting the composition of the DP with product activity and stability. Provide data supporting the criticality of quality attributes such as the quantity and relative abundance of intact, functional [redacted] as quantified by SEC-UPLC, RP-HPLC and cIEF with regards to potency and stability. Additionally, address the following comments regarding your characterization results:
    a. The 2D gel electrophoresis/nano-LC/ES-MS/MS analysis indicates that many of the analyzed spots contain [redacted] Regarding this observation:
        i. Further confirm the identity of these spots, considering that [redacted] have high degree of similarity
        ii. Provide a justification for why there appears to be more [redacted] in your DP considering that the botanical raw materials is pineapple stem.
        iii. Considering that [redacted] has different properties compared to [redacted] and considering that the [redacted], provide an assessment of how the current control strategy is adequate and sufficient to ensure lot-to-lot consistency [redacted].
    b. The cIEF analysis indicates that the samples from the RP-HPLC groups [redacted] properly. Therefore, cIEF analysis of these samples are likely to miss several peaks. Provide additional data to fully characterize the cIEF profile of the drug product and support the identity of each of the peak groups included in the release specification.

33. Regarding the proposed protocol for qualification of future NexoBrid in-house reference standard (RS):
    a. The information on qualification and requalification of RS did not include a protocol, which should identify the qualification/requalification program in detail, including testing frequency, trending activities, information on the RS and any other internal controls against which qualification/requalification would occur, analytical methods, etc. Additionally, clarify your intended reporting strategy post-licensure for the introduction of new RS.
    b. Clarify if the acceptance criteria for selecting a new RS provided in Table 95 are final or whether you intend to update the range as you release more batches of NexoBrid drug product.
    c. For the [redacted], clarify how you intend to determine the true value of the RS with a high degree of confidence, such as the using an appropriate statistical analysis. The approach to be used for the

assignment of a potency of 100% should include requirements such as a narrow acceptable % potency range to ensure control over product drift.

34. Table 8 of Section P.2.2 [redacted] The text refers to a study performed to support the [redacted] g overfill for both the 2 g and the 5 g presentations. However, the results provided in Table 8 suggest that the 5 g batches used in the study were filled with [redacted] g and not [redacted] g. Provide data to support the [redacted] g overfill of the 5 g presentation using batches filled with [redacted] g of NexoBrid Powder or provide scientific justification for the use of [redacted] g batches to support the [redacted] g overfill. Additionally, in your January 25, 2021 information request response you state "since the implementation of the [redacted] g fill weight, over 20 batches were manufactured and met the defined release limits and acceptance criteria, including the uniformity of content test"; these data should be provided to support process consistency for the [redacted] g fill weight.

35. Section P.3, states that a [redacted] However, it is unclear from the process description [redacted] rovide validation data for each configuration. A minimum and a maximum number of [redacted] and a minimum and maximum number of [redacted] should be included as process controls based on validation data. Include this information in section P.3.

36. Section P.3.4 states that "[redacted] However, you did not provide data to support the validation of these steps (i.e., [redacted]) in the process validation report. Since these are critical operational parameters, provide data to support the consistency of this step.

37. [redacted]

38. [redacted]

(b) (4)

FACILITY INSPECTIONS

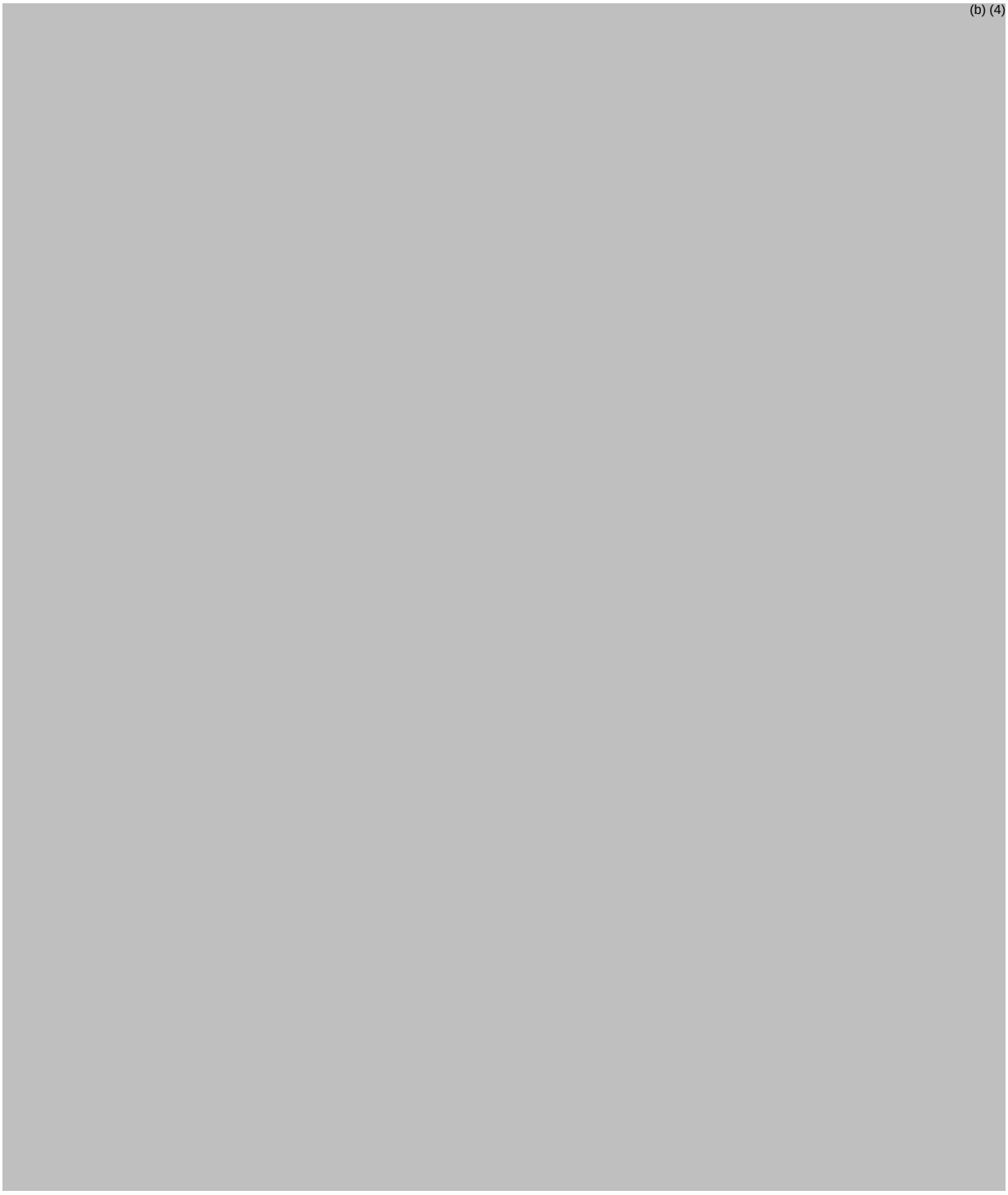
41. An inspection of the Challenge Bioproducts Company Ltd. (FEI: 3004282026), Drug Substance Intermediate manufacturing facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. For more information, please see the FDA guidances related to COVID 19.

42. An inspection of the MediWound Ltd. (FEI: 3003889199), Drug Substance, Drug Product, and Gel Vehicle manufacturing facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. For more information, please see the FDA guidances related to COVID 19.

CLINICAL SITE INSPECTIONS

43. During routine PDUFA and for-cause good clinical practice (GCP) inspections for Protocol MW2010-03-02, significant issues related to the conduct of the trial and GCP noncompliance were observed that impact the reliability of the eschar removal and wound closure assessments made by the first and second blinded assessors. The following significant issues were noted during inspections:

(b) (4)



In summary, based on inspection observations, this study was not conducted in accordance with the protocol and current GCP standards, making the data generated from the inspected sites of poor quality. Moreover, because of the significant unblinding events that occurred during the conduct of the study, the study data generated should be evaluated as if they were obtained from an open label study. Provide your

perspective on how these inspection observations impact the interpretability of the efficacy findings in Study MW2010-03-02.

PRESCRIBING INFORMATION

39. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

PROPRIETARY NAME

40. Please refer to correspondence dated, September 25, 2020 which addresses the proposed proprietary name, NexoBrid. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

41. Describe in detail any significant changes or findings in the safety profile.

42. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    - Present tabulations of the new safety data combined with the original application data.
    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

43. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

44. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

45. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

46. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

47. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

48. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Botanical Raw Materials

49. We acknowledge you added chemical and biological assays to the release specifications for BRM in your response to the IR dated January 25, 2021. In addition, you provided your justifications of not including the tests of pesticide residuals, aflatoxins, and elemental impurities in the proposed release specifications for BRM. However, as discussed in the pre-BLA meeting dated November 14, 2019 and FDA's IR dated December 19, 2020, quality control starts with the BRM. Therefore, we recommend for future manufacturing, that you follow USP <561> to conduct the tests and establish acceptance criteria for aflatoxins and follow USP <561> and the local regulations for pesticides (provide details on what local standards entail and what pesticides/herbicides were used during the cultivation of the pineapples and weed control for the pineapples used for the production of BSP). Also, clarify if the tests included in the BRM release specifications will cover all pesticides/herbicides used); USP <61> and <62> for microbial limits; USP <232> and <233> for elemental impurities.

50. You claimed that farmers that are qualified to supply pineapple stems for the production of BSP follow Taiwan Good Agricultural Practice (TGAP). In addition, you also claimed that "The following pesticides are used at the early stages of growth of the pineapple plants which are used as source of the stems for the manufacture of BSP: (b) (4). (b) (4) are included in the pesticides test in USP <561>. (b) (4) are analyzed separately. In addition to these pesticides, there is the possibility that other pesticides from surrounding farms could contaminate the pineapple plants." It appears that on p.10-13 and p.22 of the TGAP, 2007 submitted to the FDA, some pesticides and herbicides listed are not included in the list mentioned above, and are not listed in the USP <561> or Ph. Eur 2.8.13. Please clarify what pesticides and herbicides are used during the cultivation of the pineapples and weed control for pineapples used for the production of BSP. As well, clarify if tests conducted on the BRM will cover all pesticides and herbicides used.

51. We acknowledge you provided cultivar composition analysis of BSP batches manufactured between 2011 and 2019 (3.2.S.2.3.1.1.3.6 of the amendment). For future manufacturing, we recommend you develop strategies and acceptance criteria to determine how the cultivars will be pooled to produce individual batches of BSP and drug product.

52. We acknowledge you provided a "List of farmers provided (b) (4) BRM used for production of BSP used for production of NexoBrid DP batches used in the phase 3 study MW2010-03-02 (DETECT)" in your amendment. However, batch records along with batch analysis of BRM used to produce phase 3 batches were not provided. We recommend you provide batch analysis of BRM following the originally proposed BRM release specifications (the released specification submitted in the original BLA). In addition, please clarify whether BRM from the phase 3 BSP and drug product batches are available. If so, as recommended in the pre-BLA meeting dated November 19, 2019 and outlined in the IR dated December 19, 2020, we recommend you analyze the BRM used for phase 3 BSP and drug product production to establish acceptance criteria for pesticides, aflatoxins, microbial limits and elemental impurities in the BRM release specifications.

53. In the 3.2.S.2.3.1.2.3 of the amendment, the description of the list of fertilizers used was unclear. Please provide the complete list of fertilizers used and clarify what organic fertilizers were used.

54. Please submit the following documents related to Good Agricultural and Collection Practices (GACP) to the Agency to review:
    a. CBC's GACP Standard Operating Procedures (SOP). In addition, please clarify how it is implemented in addition to TGAP.
    b. CBC's SOP for pineapple cultivation record (QP16-A)

c. CBC's shipping procedure (QP-17)
d. CBC's SOP for receipt of (b) (4) pineapple stems (GP05)
e. Identification Method of Stem Cultivar by Characteristics ((b) (4) stem sample (b) (4)) (RS-20)
f. SOP for appearance assay of pineapple stems ((b) (4) stem vs. (b) (4) specimen)

55. In addition to the control of BRM, we recommend you conduct orthogonal analysis of chemical and biological data produced in BSP and/or drug substance (if applicable) and final product that were used in phase 3 trials. Subsequently, correlate the batch analysis to clinical outcomes to assess treatment-by-batch interactions and ultimately to ensure batch-to-batch consistency.

Clinical Pharmacology

56. The completed maximal use study would not support the labeling that was submitted with the BLA application. If you desire to seek the labeling which is currently proposed, then you will need to conduct a new maximal use study designed to address the systemic safety of your product and support the proposed dosing regimens. In particular, you should ensure that you study adequate numbers of patients that are treated with two applications of the product who have % total body surface area (TBSA) within the upper range and are treated with doses within the upper range to support systemic safety and desired labeling.

57. If you choose to proceed with labeling in accordance with the currently completed maximal use study, then labeling will be restrictive in terms of number of applications, %TBSA and total dosing.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 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 in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. 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 what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products.*

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jennifer Harmon, Regulatory Project Manager, at 240-402-4880.

Sincerely,

{See appended electronic signature page}

Julie G. Beitz, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIE G BEITZ
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