CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761192Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 27, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Leslie Rivera Rosado, PhD, Review Chief OBP/Division of Biotechnology Review and Research 4
Application:	BLA 761192
Applicant:	MediWound, Ltd
Submission Date:	July 1, 2022
Product:	NexoBrid (anacaulase-bcdb)
Dosage form(s):	For topical gel
Strength and Container-Closure:	1.94 g [or 4.85 g] anacaulase-bcdb in 2 g [or 5 g] lyophilized powder (8.8% w/w after mixing with co-packaged gel)
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information (submitted on December 23, 2022), and container labels and carton labeling (submitted on December 21, 2022, via email) were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information (submitted on December 23, 2022), and container labels and carton labeling (submitted on December 21, 2022 via email) were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling Prescribing Information (submitted on July 1, 2022 \\CDSESUB1\EVSPROD\bla761192\0036\m1\us\114-labeling\draft\labeling\draft-labeling-text-pdf.pdf**)**

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the proper name anacaulase-bcdb. If space permits, consider adding the dosage form outside of the parenthesis and/or below the proper name, "for topical gel".
NexoBrid
(anacaulase-bcdb)
For topical gel, 8.8%
For Topical Use Only

For the gel container label, the applicant did not add the primary expression of strength "8.8%". Since the primary expression of strength is after mixing and the gel jar will contain the final mixed product, revise "For use with anacaulase-bcdb lyophilized powder, for topical gel (8.8% w/w after mixing)". *The Applicant revised as requested*

For the powder container label, the applicant neither added the dosage form "for topical gel" nor the primary expression of strength "8.8%". Since the primary expression of strength is after mixing, then it is agreeable to not include "8.8%" on the lyophilized container label. However, the dosage form should appear on the lyophilized container label along with other important information on the principal display panel as follows:
"NexoBrid
(anacaulase-bcdb)
For topical gel

1.94 g [or 4.85 g] anacaulase-bcdb in 2 g [or 5 g] lyophilized powder

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

For Topical Use Only" *The Applicant revised as requested*

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The Applicant's name as listed in field 2 of Form FDA 356h is the licensed applicant, licensed manufacturer, or manufacturer. Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h using the qualifying phrase 'Manufactured by:".
Manufactured by: MediWound, Ltd
42 Hayarkon Street Industrial Zone
Yavne, Israel

The Applicant revised the manufacturer's statement as requested; however, they also added (b) (4) (b) (4) (b) (4) (b) (4). The U.S. license number placeholder should appear with the licensed applicant information. Revise the manufacturer (licensed applicant) and distributor's statement as follows:

"Manufactured by: MediWound, Ltd
42 Hayarkon Street Industrial Zone
Yavne, Israel
U.S. License Number xxxx
for: Vericel Corporation
64 Sidney St
Cambridge MA 02139"
The Applicant revised as requested

Lot number or other lot identification (container label)	**Acceptable**

[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The primary expression of strength is % w/w and is based on the amount of active botanical.

1.94 g botanical drug product (b) (4) / [20 g GV + 2 g powder = 22.0 g total weight] = 8.8%
4.85 g botanical drug product (b) (4) / [50 g GV + 5 g powder = 55 g total weight] = 8.8%

Add the primary expression of strength to the principal display panel following the dosage form as follows:

NexoBrid
(anacaulase-bcdb)
For topical gel, 8.8%

See recommendation for the lyophilized powder container label (above) in proper name recommendation and carton labeling in proper name recommendation (below in package label eval)

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	☐ Yes

	☐ No ☒ N/A

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

NDC numbers **(container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the statement on the back panel of the containers and cartons from (b) (4) to read as follows: "For one patient and one application"
The Applicant revised as requested

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to	✓ Yes ☐ No

Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	☐ N/A

Comment/Recommendation: Lyophilized powder amount should be the weight of anacaulase-bcdb (active component: 97% of 2 g or 5 g) not including overfill. Gel vehicle labeled amount will not include overfill.

For the lyophilized powder container label, revise the net weight from '(b) (4) (b) (4)r' and from '(b) (4)' to read as: "1.94 g [or 4.85 g] anacaulase-bcdb in 2 g [or 5 g] lyophilized powder"
The Applicant revised as requested

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider revising from "(b) (4) (b) (4)" to "Dosage: See Prescribing Information"
The Applicant revised as requested

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the storage statement as follows:

"Store and transport NexoBrid upright and refrigerated at 2°C to 8°C (36 °F to 46 °F) in the original carton to protect from light. DO NOT FREEZE" *The Applicant revised as requested*

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the statement on the back panel of the containers and cartons from [redacted] (b) (4) " to "Use sterile instrument to thoroughly mix powder in gel jar" *The Applicant revised as requested*

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the proper name anacaulase-bcdb. If space permits, consider adding the dosage form outside of the parenthesis and/or below the proper name, "for topical gel". NexoBrid (anacaulase-bcdb) For topical gel, 8.8% For Topical Use Only *The Applicant revised as requested*

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The Applicant's name as listed in field 2 of Form FDA 356h is the licensed applicant, licensed manufacturer, or manufacturer. Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h using the qualifying phrase 'Manufactured by:".
Manufactured by: MediWound, Ltd
42 Hayarkon Street Industrial Zone
Yavne, Israel

The Applicant revised the manufacturer's statement as requested; however, they also added a (b) (4) (b) (4) (b) (4) (b) (4). The U.S. license number placeholder should appear with the licensed applicant information. Revise the manufacturer (licensed applicant) and distributor's statement as follows:

"Manufactured by: MediWound, Ltd
42 Hayarkon Street Industrial Zone
Yavne, Israel
U.S. License Number xxxx
for: Vericel Corporation
64 Sidney St
Cambridge MA 02139"
The Applicant revised as requested

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the words "No Preservative" to the panel with the ingredient information *The Applicant revised as requested*

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the contents statement as follows:
"Contents: 1 single-dose vial containing 1.94 g [or 4.85 g] of anacaulase-bcdb in 2 g [or 5 g] of powder
1 single-dose jar containing 20 g [or 50 g] of sterile gel vehicle"

Thus delete (b) (4)
The Applicant revised as requested

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: see container comments for primary expression of strength

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No

	☐ N/A

Comment/Recommendation: Revise the storage statement as follows: Store and transport NexoBrid upright and refrigerated at 2°C to 8°C (36 °F to 46 °F) in the original carton to protect from light. DO NOT FREEZE. *The Applicant revised as requested*

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise ingredient list to:

"Each vial contains 1.94 g [or 4.85 g] of anacaulase-bcdb in 2 g [or 5 g] of lyophilized powder and is composed mainly (80% to 95% w/w) of the proteins: stem bromelain, ananain, jacalin-like lectin, bromelain inhibitors, and phytocystatin inhibitor; and saccharides, as both free monosaccharides and the N-linked glycan of stem bromelain, and small molecule metabolites. The drug substance includes inactive buffer components containing acetic acid, ammonium sulfate and Water for Injection. Each gram of lyophilized powder contains 0.97 g of anacaulase-bcdb.

Each jar contains 20 g [or 50 g] of sterile, preservative-free gel vehicle containing carbomer 980, dibasic sodium phosphate, sodium hydroxide, and Water for Injection."
The Applicant revised as requested

Confirm if (b) (4) meet the definition of the USP monograph Dibasic sodium phosphate. *Applicant's response: Revised the ingredient list as recommended above text. Yes,* (b) (4) *meet the definition of the USP monograph dibasic sodium phosphate.*

Revise from " (b) (4) to read as a total net weight after mixing as "Net weight is 22 grams (after mixing)" or "Net weight is 55 grams (after mixing)" *The Applicant revised as requested*

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the source of the API to the carton labeling as follows: "Proteolytic enzymes extracted from the stems of pineapples (Ananas comosus (L.) Merr.)"
The Applicant revised as requested

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: *Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for anacaulase products (i.e., there is no specific test method described in regulation for anacaulase products that*

establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for NexoBrid because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling."

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider revising the preparation instructions as follows: "Prior to application: Use a sterile instrument to thoroughly mix the powder in the gel vehicle. Discard mixture if not used within 15 minutes of preparation.

After application: NexoBrid is for only one patient and one application. Discard any unused portion." *The Applicant revised as requested*

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	☐ Yes ☐ No ☒ N/A

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise from "(b) (4) " to read as a total net weight after mixing as "Net weight is 22 grams (after mixing)" or "Net weight is 55 grams (after mixing)" *The Applicant revised as requested*

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes

	☐ No ☐ N/A

Comment/Recommendation: Consider revising from (b) (4) (b) (4) to "Dosage: See prescribing information" *The Applicant revised as requested*

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: added the dosage form "for topical gel". The term "for" is included to indicate that the solid (e.g., powder) is to be added to, dissolved in, or suspended in a liquid (e.g., gel) during preparation. The route of administration (for topical use) need not be repeated here in the product title after the dosage form since the route of administration 'topical' precedes the dosage form 'gel'. See Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018) *The Applicant revised as requested*

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Primary expression of strength as 8.8% *The Applicant revised as requested*

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**

Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: revised to the corrected dosage form and to the customary placement of the dosage form for recently approved FDA labeling, the primary expression of strength as %w/w, and add the identifying characteristics of the lyophilized powder and gel vehicle *The Applicant revised as requested*

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: *The amount of a botanical drug substance should generally be expressed as the absolute dry weight of a processed botanical substance. When the active constituents or other chemical constituents are known and measurable, the amount in which they are present in the botanical drug substance should be declared. The composition of multi-plant drug substances, in terms of the relative ratio of the individually processed botanical drug substances or of the botanical raw materials before processing (as applicable), should be expressed.*
the first paragraph describes the drug substance, anacaulase-bcdb *The Applicant revised as requested*
removed (b) (4) which is not required for this section *The Applicant revised as requested*
provided the amount of anacaulase-bcdb per gram of lyophilized powder *The Applicant revised as requested*
Provided the pH of the mixture please confirm *The Applicant revised as requested*
Confirm if (b) (4) meets the definition of the USP monograph Dibasic sodium phosphate. *The Applicant confirmed*

The Applicant revised the identifying characteristics of the mixture from (b) (4) *to "yellowish white to light brown opaque gel". This revision is acceptable.*

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: provided the primary expression of strength, 8.8%, the identifying characteristics of the lyophilized powder and gel vehicle, the amount of anacaulase-bcdb per vial *The Applicant revised as requested*

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: the name and address of the manufacturer (applicant on form FDA 356h field 2) has been added along with a placeholder for the US license

Manufactured by:
MediWound, Ltd
42 Hayarkon StreetYavne, Israel 8122745
U.S. License Number
The Applicant revised as requested. The Applicant also provided the distributor.

Medication Guide Evaluation (N/A)
Patient Information Labeling Evaluation (N/A)
Instructions for Use Evaluation (N/A)

APPENDIX C. Acceptable Labels and Labeling
Prescribing Information (submitted on December 23, 2022
\\CDSESUB1\EVSPROD\bla761192\0046\m1\us\114-labeling\draft\labeling\draft-labeling-text-pdf.pdf)

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 12/27/2022 02:31:26PM
GUID: 50814c7000007a3d59329f660d8ddf02

Leslie Rivera-Rosado

Digitally signed by Leslie Rivera-Rosado
Date: 12/28/2022 10:45:49AM
GUID: 508da7420002bb7d3e8efdb59ecfa84e

Recommendation: Approval

BLA Number: 761192 (resubmission)
Assessment Number: Second cycle
Assessment Date: December 14, 2022

Drug Name/Dosage Form	NexoBrid (anacaulase-bcdb), for topical gel
Strength/Potency	8.8% gel
Route of Administration	Topical
Rx/OTC dispensed	Rx
Indication	Eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns
Applicant/Sponsor	MediWound Ltd. 42 Hayarkon Street, Yavne, Israel 8122745
US agent	Michael Halpin 64 Sidney Street, Cambridge, MA 02139 mhalpin@vcel.com Telephone number: 617-588-5662

Product Overview:

NexoBrid (anacaulase-bcdb), is a mixture of proteins extracted from the stems of the pineapple plant (*Ananas comosus* [L.] *Merr.*).

NexoBrid drug product (DP) is comprised of two components, a sterile lyophilized powder, and a sterile Gel Vehicle for preparation of a gel for topical use. The NexoBrid DP is lyophilized DS powder filled into glass vials. NexoBrid DP powder is provided in 50 mL glass vials containing either 2 g or 5 g of the lyophilized powder. Each gram of lyophilized powder contains 0.97 g of anacaulase-bcdb. The Gel Vehicle is provided in 150 mL glass jars containing either 20 g or 50 g of the gel. Prior to administration, 2 g or 5 g of NexoBrid powder is mixed with 20 g or 50 g Gel Vehicle to produce an 8.8% w/w gel for topical application.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Botanical material	Yen-Ming Chan (original submission) Charles Wu (CR response, resubmission)	CDER/OPQ/ONDP Botanical Team
Drug Substance (DS)	Leopold Kong (original submission) Andrea Franco (CR response, resubmission)	CDER/OPQ/OBP/DBRR IV
Drug Product (DP)		
Labeling	CAPT Vicky Borders-Hemphill	CDER/OPQ/OBP
Microbiology and Facilities	Lindsey Brown (DS) Wendy Tan (DP)	CDER/OPQ/OPMA/DBM
Team Leads	LCDR Leslie A. Rivera Rosado (Product Quality) Maxwell Van Tassel (Micro) Zhong Li (Facilities)	CDER/OPQ/OBP/DBRR IV CDER/OPQ/OPMA CDER/OPQ/OPMA/DBM
Application Technical Lead	LCDR Leslie A. Rivera Rosado	CDER/OPQ/OBP/DBRR IV
Regulatory Business Project Manager	Anita Brown	CDER/OPQ/OPRO

Multidisciplinary Assessment Team:

RPM/TL	Jennifer Harmon/ Margaret Kober
DDD Director	Julie Beitz
CDTL	David Kettl
Clinical	Brenda Carr/ Shera Schreiber
Non-Clinical	Jianyong Wang/Barbara Hill
ClinPharm	Anand Balakrishnan/Chinmay Shukla (TL)
Biostatistics	Kathleen Fritsch/Mohamed Alosh (TL)

1. Names:

a. Proprietary Name: NexoBrid
b. Trade Name: NexoBrid
c. Non-Proprietary Name: Anacaulase (Proper name assigned by the FDA. USAN names are not assigned to mixtures)

Anacaulase
Ana-: Ananas comosus (botanical name)
-caul-: Caulis (latin for stem)
-ase: enzymes (partially purified mixture of enzymes, bromelain and ananain)

d. CAS Name: CAS RN 68917-26-0
e. Common Name: "Concentrate of proteolytic enzymes enriched in Bromelain"
f. INN Name: INN cannot be assigned to a heterogeneous mixture of proteolytic enzymes.
g. Compendial Name: N/A
h. OBP systematic name[1]: PROT P80884 (ANAN_ANACO) & PROT Q9S8M1(Q9S8M1_ANACO) & PROT O23791 (BROM1_ANACO) & PROT P14518 (BROM2_ANACO) [MEDIWOUND]

Nomenclature used throughout the dossier

Nomenclature Used	Description
Drug Substance	
Concentrate of proteolytic enzymes enriched in Bromelain	Common name (proposed)
NexoBrid Drug Substance	Internal code used throughout dossier
Starting Material	
Pineapple Plant stems	*Ananas comosus* [L.] Merr. botanical raw material

[1] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

Bromelain Special Production (Bromelain SP)	Bromelain SP is extracted from pineapple stems and is used as the intermediate Drug substance

Classification of the Pineapple Plant

Order	Bromeliales
Family	Bromoeliaceae
Genus	Ananas P. Mill
Species	*Ananas comosus* [L.] Merr.

Submissions Assessed:

Submission(s) Reviewed	Document Date	Review Completed (Yes/No)
BLA 761192/36 (Resubmission)	7/1/2022	Yes
BLA 761192/37 Response to OPMA/DBM Information Request (facilities)	7/27/2022	Yes
BLA 761192/38 Response to OPMA/DBM Information Request (micro)	11/4/2022	Yes
BLA 761192/39 Response to OPMA/DBM Information Request (micro)	11/22/2022	Yes
BLA 761192/40 Response to OBP Information Request	11/29/2022	Yes
BLA 761192/41 Response to OBP and OPMA/DBM Information Request	12/12/2022	Yes
BLA 761192/43 Response to OPMA/DBM Information Request	12/20/2022	Yes
BLA 761192/45 Response to OPMA/DBM Information Request	12/22/2022	Yes

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

   A. Drug Master Files (DMF)
   No DMFs are referenced in the resubmission. Refer to the review memo for the original submission.

   B. Other documents

Document	Application Number	Description
Original BLA submission	BLA 761192	Original BLA submission received 6/29/2020 and all relevant BLA amendments submitted between 6/29/2020 and 7/1/2022.

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:

The Applicant claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c) as the biologic product occurs naturally in the environment and approval of the application does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the

environment. The Applicant states that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. *The claim of categorical exclusion is deemed acceptable.*

Executive Summary

MediWound Ltd (MediWound) submitted the Biologic License Application (BLA), 761192, for NexoBrid (formerly Debrase®) on 29 June 2020. NexoBrid is indicated for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns. MediWound was issued a Complete Response Letter for BLA 761192, dated 25 June 2021. In accordance with 21 CFR 601.3(b)(1) MediWound provided a resubmission of the BLA 761192 for NexoBrid to address the deficiencies listed in the Complete Response Letter.

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761192 for NexoBrid manufactured by MediWound, Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of NexoBrid is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Intermediate Drug Substance:
    - Challenge Bioproducts Corporation Ltd (CBC)
      17, Tou-Kong 12 Road
      Tou-Liu Industrial Park
      Tou-Liu City, Yun-lin Hsien, Taiwan
      FDA EIN: 3004282026
  - Drug Substance and Drug Product:
    - MediWound Ltd
      42 Hayarkon St.,
      Yavne 8122745, Israel
      FDA EIN: 3003889199
- Fill size and dosage form: 2 g or 5 g of lyophilized NexoBrid Drug Product (DP) powder and 20 g or 50 g of a Gel Vehicle. For topical gel.
- Dating period:
  - Drug Product: 36 months: 5°C ± 3°C
  - Intermediate Drug Substance: (b) (4) months: (b) (4) °C ± (b) (4) °C

(b) (4)

- For packaged products:
  - Drug Product: 36 months: 5°C ± 3°C
  - Gel Vehicle: 36 months: 5°C ± 3°C

- Exempt from lot release
  - Yes
  - Rationale, if exempted: The overall control strategy, including manufacturing and release controls, is adequate to control lot-to-lot variability and product quality over the proposed shelf-life.

C. Benefit/Risk Considerations:

The drug substance in NexoBrid, anacaulase-bcdb, is a mixture of proteolytic enzymes extracted from the stems of pineapple plants (*Ananas comosus* [L.] *Merr.*) that has been sterile filtered and lyophilized. Anacaulase-bcdb is composed mainly (80% to 95% w/w) of the proteins: stem bromelain, ananain, jacalin-like lectin, bromelain inhibitors, and phytocystatin inhibitor; and saccharides, as both free monosaccharides and the N-linked glycan of stem bromelain, and small molecule metabolites. The drug substance includes inactive buffer components containing acetic acid, ammonium sulfate, and Water for Injection. Each gram of lyophilized powder contains 0.97 grams of anacaulase-bcdb.

NexoBrid (anacaulase-bcdb) for topical gel is a botanical drug product supplied as a sterile, preservative-free, lyophilized powder in a single-dose glass vial that must be mixed in a gel vehicle supplied in a single-dose glass jar prior to application. Mixture of either 2 grams of lyophilized powder (containing 1.94 grams of anacaulase-bcdb) or 5 grams of lyophilized powder (containing 4.85 grams of anacaulase-bcdb) in 20 grams or 50 grams of gel vehicle, respectively, provides an 8.8% w/w, yellowish white to light brown opaque gel for topical use. The pH of the topical gel mixture is approximately 6.2 to 6.7.

The co-packaged 20 gram or 50 gram jar of the sterile, preservative-free gel vehicle contains carbomer 980, dibasic sodium phosphate, sodium hydroxide, and Water for Injection.

The NexoBrid powder is mixed with the provided gel vehicle for topical administration within 15 minutes of mixing. NexoBrid is indicated for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns. Eschar removal, "debridement", is considered a critical initial stage of the comprehensive burn care process. Early and rapid debridement of eschar is essential to initiate the wound healing process, to allow clinical visual evaluation of burn severity and depth, preserve viable tissue, and prevent further complications. The mechanism of action (MoA) of NexoBrid is mediated by the proteolytic activity of its enzymes and is associated with selective debridement of eschar and denatured collagen.

The botanical raw material (BRM), pineapple stems, are harvested from pineapple plants grown for human consumption by qualified farmers following Taiwan Good Agriculture Practice (TGAP), as part of Good Agricultural and Collection Practices (GACP). The BRM is authenticated (morphologically and biochemically) and tested and controlled for the presence of foreign matter, bioburden, and other contaminants (heavy metals, pesticide residues, aflatoxins). The active components of the product are extracted from the BRM and partially purified (known as the Bromelain Special Production (BSP) or drug substance intermediate). The manufacturing process is performed (b) (4)

BSP is controlled for

(b) (4)

(b) (4)

(b) (4)

The entire manufacturing process and process controls are designed to control contamination and prevent product degradation.

Although endotoxins testing is not required for finished drug products for topical administration, NexoBrid's indication is for burn wound debridement, and therefore, there is potential that endotoxins could get into the bloodstream. However, due to the proteolytic activity of the product, there are no reliable methods to test endotoxin contents in the finished drug product. Therefore, the following strategies were put in place to mitigate endotoxin contamination:

(b) (4)

Routine bioburden testing is currently done by using (b) (4)

(b) (4)

(b) (4) Therefore, MediWound agreed to submit method suitability data for the bioburden test using the (b) (4) BSP as a post-marketing commitment (PMC).

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Challenge Bioproducts Company Ltd. (FEI 3004282026), proposed for bromelain special product DS intermediate manufacture. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for MediWound Ltd. (FEI 3003889199), proposed for Nexobrid DS manufacture All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

Submit the final method suitability testing results for the bioburden test for drug substance release using all compendial challenge organisms with (b) (4) (b) (4)

Final Report Submission: 05/2023

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy
Purity and identification (by SEC-UPLC)	Bioactivity (efficacy), immunogenicity, and safety	Botanical Raw material (BRM), manufacturing process	(b) (4)
Purity (by RP-HPLC)	Bioactivity (efficacy), immunogenicity, and safety	Intrinsic to the protein mixture, raw material, and manufacturing process	
Biological Activity (Potency)	Bioactivity (efficacy) and safety	Raw material, Manufacturing Process, and Storage	

B. Drug Substance Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy
Appearance (Color/ Clarity)	Safety	Intrinsic to the product	(b) (4)
Protein concentration (Content)	Bioactivity (efficacy) and safety	Raw material, Manufacturing process	
pH	Bioactivity and stability	Manufacturing	

CQA (type)	Risk	Origin	Control Strategy
		Process and formulation	
Total viable aerobic count (Microbial Control)	Safety, Purity	Raw material, Manufacturing Process	(b) (4)
Test for specific microorganism (Microbial Control)	Safety, Purity	Raw material, Manufacturing Process	
Endotoxin	Safety, Purity	Raw material, Manufacturing Process	
(b) (4) (Microbial Control)	Safety, Purity	Raw material, Manufacturing Process	
(b) (4) (Viral Control)	Safety, Purity	Raw material, Manufacturing Process	
(b) (4) (Impurity)	Potential impact to safety	Raw material, Manufacturing Process	
(b) (4) (Impurity)	Potential impact to safety	Raw material, Manufacturing Process	
(b) (4) (Impurity)	Potential impact to safety	Raw material, Manufacturing Process	
(b) (4) (Impurity)	Potential impact to safety	Raw material, Manufacturing Process	
Water content	High water content may cause protein degradation during storage can affect the efficacy and safety.	Lyophilization process	

- **Description**:
  Bromelain Special Production (BSP) is an extract obtained from pineapple stems (*Ananas comosus* [L.] *Merr.*) through (b) (4) filtration and lyophilization. Further processing of BSP yields NexoBrid drug substance (DS). NexoBrid DS comprises a partially purified

mixture of botanical proteins (proteolytic enzymes) extracted from the stems of the pineapple plant.

The DS is primarily composed of proteins (80-95%), saccharides (b) (4) (b) (4) (b) (4) [buffer components ((b) (4) acetic acid, (b) (4) ammonium sulfate), small molecule metabolites (b) (4) (b) (4)

The primary protein components identified by characterization of the DS and available literature are summarized below. (b) (4)

Protein Component	Characteristics
Stem Bromelain (b) (4)	(b) (4)
Ananain (b) (4)	
Jacalin-like Lectin	
Bromelain Inhibitors	
Phytocystatin	
(b) (4	

Protein Component	Characteristics
	(b) (4)

- Mechanism of Action (MoA): NexoBrid is intended to debride burn eschars. The primary component of burn eschars is denatured collagen or "gelatin". NexoBrid has proteolytic activity against collagens type I and IV, and higher activity against gelatin. The Applicant emphasizes that this difference in activity is clinically relevant since burn eschar is primarily composed of "gelatin".

- Potency Assays: Monitoring of NexoBrid proteolytic activity is performed via a combination of *in vitro* assays: (a) (b) (4) activity, (b) (b) (4) activity and (c) (b) (4) activity. These assays are performed on the DP due to the instability of the DS.

(b) (4)

- Reference Materials: Refer to Drug Product Reference Standard section below.

- Critical starting materials or intermediates:

(b) (4)

(b) (4)

- Manufacturing process summary:

(b) (4)

- Container closure:

(b) (4)

- Dating period and storage conditions:

(b) (4)

C. Drug Product [NexoBrid] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	CQA	Risk	Origin	Control Strategy
Identification	FT-IR UV Spectrum	Control of batch-to-batch variability, efficacy/safety	Botanical raw material (BRM), intrinsic to the protein mixture	(b) (4)
Activity/potency	Potency: (b) (4) Assay (b) (4)	Variability in proteolytic activity will affect the efficacy and safety of the product.	Intrinsic to the protein mixture, raw material, Manufacturing process, storage/stability	

CQA (type)	CQA	Risk	Origin	Control Strategy
Purity Profile (Product-related variants/impurities)	SEC-HPLC RP-HPLC cIEF	Potential impact to efficacy, Immunogenicity, and Safety.	Intrinsic to the protein mixture, BRM, production process (including lyophilization process), storage	(b) (4)
Assay	Protein Content (protein concentration)	Assay assures the strength of the formulation, directly linked to safety and efficacy.	BRM, manufacturing process	
Excipient testing	Acetic Acid	Efficacy	Formulation	
Sterility	Sterile	Presence of microorganisms may affect the safety and integrity of the product.	Manufacturing process, raw materials, filtration steps and environment during powder filling	
Content Composition	Water content	High water content may cause protein degradation during shelf life which can affect the efficacy and safety.	Lyophilization process and powder filling Storage	
Impurities	(b) (4)	Safety	Manufacturing process	
Potential Contaminants		Safety	BRM, raw materials	
		Safety	BRM	
		Safety	BRM	

Gel Vehicle (GV)

CQA	Risk	Origin	Control Strategy
Appearance	Efficacy	Formulation	(b) (4)
pH			
Homogeneity			
Viscosity			

Drug Product + Gel vehicle mixture

CQA	Risk	Origin	Control Strategy
Appearance	Efficacy	Formulation	(b) (4)
pH			
Homogeneity			
Viscosity			
Reconstitution time			

- **Potency and Strength:** 2 g or 5 g NexoBrid lyophilized powder in a vial (97% of botanical components and 3% excipients)

- **Summary of Product Design:** NexoBrid will be supplied as a 50 mL glass vial containing 2 g or 5 g of a lyophilized NexoBrid DP powder together with a 150 mL glass jar containing 20 g or 50 g of a Gel Vehicle, respectively, intended for mixing the powder before administration. One vial of NexoBrid DP and 1 jar of Gel Vehicle of the corresponding size are supplied together in a cardboard carton kit. After mixing, both dose-size presentations contain the same concentration (0.088 g/g or 8.8% w/w) of active substance (anacaulase).
  - Each gram of lyophilized powder contains 0.97 g of anacaulase
    - 2 g of DP power mixed in 20 g GV = 1.94 g anacaulase / 22.0 g total weight after mixing x 100% = 8.8%
    - 5 g of DP power mixed in 50 g GV = 4.85 g anacaulase/ 55.0 g total weight after mixing x 100%= 8.8%

- **List of Excipients:**

Composition of NexoBrid Product[a]

Component	Concentration	Content in 2 g Presentation	Content in 5 g Presentation	Grade	Function
NexoBrid powder	(b) (4) mg/mL[b]	(b) (4) mg	(b) (4) mg	In-house	Active Substance
Acetic acid	(b) (4) mg/mL			USP	Drug substance buffer
Ammonium Sulfate	(b) (4) mg/mL			NF	Drug substance buffer (b) (4)
(b) (4)					

Composition of Finished NexoBrid Drug Product

Presentation	Absolute dry percentage of the processed botanical substance[a]	Acetic acid Percentage[b]	Ammonium Sulfate amount[c]
2 g vial	(b) (4)		

5 g vial	[redacted]		
Grade	-	USP	NF
Function	Active substance	Drug substance buffer	Drug substance buffer [redacted]

[redacted]

Composition of Gel Vehicle

Component	% (w/w)	Content in 20 g Presentation	Content in 50 g Presentation	Grade	Function
Carbomer 980	[redacted]			NF	[redacted]
Disodium [redacted] phosphate, [redacted]				USP	
Sodium hydroxide				NF	
Water for injection				USP	

NF = National Formulary, q.s. = Quantum sufficit (a sufficient quantity), USP = United States Pharmacopeia

- **Reference Materials:**

[redacted]

New primary reference standards (PRS) and working reference standards (WRS) will be selected and qualified before the current RS expires. Future PRS and WRS qualified following the qualification protocols approved in the BLA will be submitted in annual reports.

- **Manufacturing process summary:**
NexoBrid DP is manufactured at MediWound Ltd, 42 Hayarkon St., Yavne, Israel. Manufacture of the NexoBrid DP is a standard process consisting of [redacted]

(b) (4)

- **Container closure:**
  The container for NexoBrid DP is a 50 mL, Type (b) (4) glass vial (b) (4) stoppered with (b) (4) rubber stopper and further sealed with an aluminum flip-cap.

  The container for the Gel Vehicle is a 150 mL, Type (b) (4) glass jar (b) (4) stoppered with a (b) (4) rubber stopper and further sealed with a (b) (4) screw cap.

- **Dating period and storage conditions:** The proposed shelf-life is 36 months at 5°C±3°C.

- **List of co-package components, if applicable:** Gel Vehicle in a 150 mL jar.

D. Novel Approaches/Precedents:

First botanical naturally derived biologic product licensed by CDER.

E. Any Special Product Quality Labeling Recommendations:

a. Store at 2 - 8°C protected from light.
b. Once the lyophilized powder and the gel vehicle are mixed, the product should be used within 15 minutes.

F. Establishment Information:

Function	Site Information	FEI Number	Preliminary Assessment	Final Recommendation
Manufacturing, filling, packaging, labelling, and all quality control testing of Bromelain Special Production (BSP) intermediate drug substance	**Challenge Bioproducts Company Ltd** 17, Tou-Kong 12 Road Tou-Liu Industrial Park Tou-Liu City, Yun-lin Hsien Taiwan.	3004282026	Inspection Required	Approve – based on inspection
Release testing of BSP. Manufacture, filling, packaging, labeling, and quality control testing (including both release and stability) of NexoBrid DS, DP, and Gel Vehicle.	**MediWound Ltd** 42 Hayarkon St., Yavne 8122745 Israel	3003889199	Inspection Required	Approve – based on inspection

(b) (4)	Approve – based on previous history
	Approve – based on previous history
	Approve – based on previous history

Facilities:

A pre-license inspection of the Challenge Bioproducts Co., Ltd. (FEI 3004282026), Tou-Liu City, Taiwan facility was conducted from 10/24/2022 to 10/31/2022. At the conclusion of the PLI, a 3-item FDA Form 483 was issued. The initial field recommendation is VAI. Upon review of the 483 responses, the Compliance Team concurs with the initial field recommendation of VAI.
This facility is recommended for Approval.

A pre-license inspection (PLI) of the Mediwound Ltd. (FEI 3003889199), Yaven, Israel facility was conducted from 11/7-10 and 11/13-15/2022. At the conclusion of the PLI, a 5-Item FDA Form 483 was issued. The initial field recommendation is VAI. Upon receipt and review of the 483 responses, the Compliance Team concurred with the initial field recommendation of VAI.
This facility is recommended for Approval.

G. Lifecycle Knowledge Management:

c. Drug Substance and Drug Product:

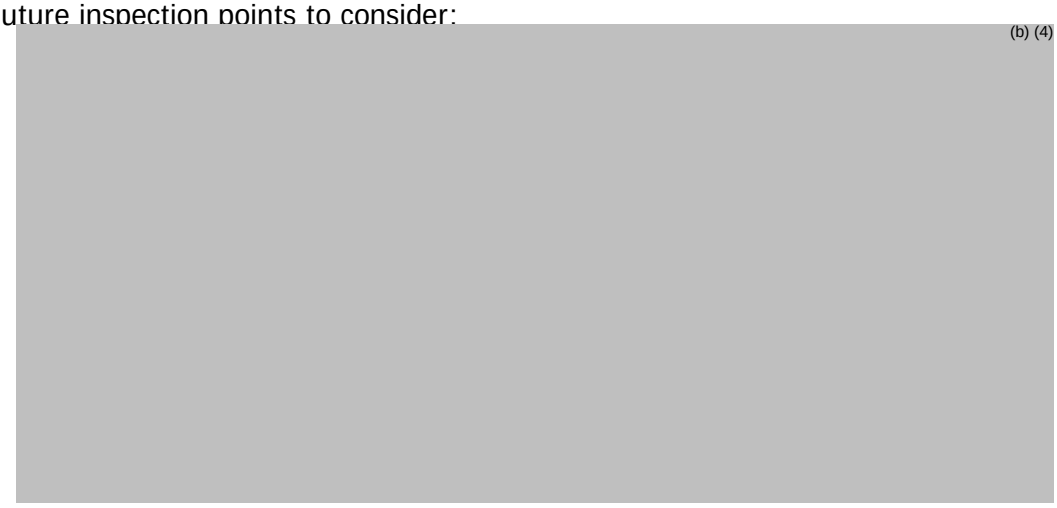
i. Protocols approved:

1. Primary and working reference standard qualification and stability protocols.
2. Post-approval stability protocols (BSP, DP, gel vehicle)

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider:

(b) (4)



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/s/

LESLIE A RIVERA-ROSADO
12/27/2022 09:54:21 AM

BB-IND:	BLA761192
SERIAL:	Supporting Document Number 36; eCTD# 0036
SUBMISSION DATE:	7/1/2022
SUBJECTS:	Response to the Complete Response Letter issued by the Agency on 6/25/2021
REVISION DATE:	11/14/2022; 12/01/2022; 12/12/2022
FROM:	Andrea Franco, Ph.D., Product Quality Assessor
THROUGH:	Leslie A. Rivera Rosado, Ph.D., Review Chief
PRODUCT:	NexoBrid
OBP Systematic Name:	PROT P80884 (ANAN_ANACO) & PROT Q9S8M1(Q9S8M1_ANACO) & PROT O23791 (BROM1_ANACO) & PROT P14518 (BROM2_ANACO) [MEDIWOUND]
INDICATION:	Eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns
ROUTE OF ADMIN.	Topical
DOSE REGIMEN:	NexoBrid may be applied to an area of up 15% total body surface area (TBSA) in one application. A second application of NexoBrid may be applied 24 hours later to same or new burn wound. The total treated area for both applications must not exceed 20% TBSA.
APPLICANT:	MediWound, Ltd
CLINICAL DIVISION:	Division of Dermatology and Dental Products

BACKGROUND

On June 29, 2020, the applicant submitted a BLA for NexoBrid. However, due to multiple deficiencies identified by OPQ and OSI, on June 25, 2021, the Agency issued a Complete Response Letter. On July 1, 2022, the applicant provided a resubmission of the BLA 761192 for NexoBrid to address all the deficiencies listed in the Complete Response Letter. Below is the assessment of the responses provided for product quality deficiencies.

REVIEW

***Assessor's Comment**: Assessment of the applicant's response to the Agency Question 1 is deferred to the Botanical Review Team. Assessments of the applicant's responses to the Agency Question 2 to Question 19 are deferred to the OPMA/DBM reviewers.*

Product quality CR comments 20 – 38 are reviewed below.

Agency Comment 20

In your January 25, 2021, response to the IR sent on December 21, 2020, you commit to provide the following data:

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Andrea Franco

Digitally signed by Andrea Franco
Date: 12/13/2022 05:00:32PM
GUID: 55798a5d00259df2b007ed28a45e075e

Leslie Rivera-Rosado

Digitally signed by Leslie Rivera-Rosado
Date: 12/15/2022 01:10:24PM
GUID: 508da7420002bb7d3e8efdb59ecfa84e

Recommendation: Complete Response

BLA Number: 761192
Assessment Number: First cycle
Assessment Date: March 23, 2021

Drug Name/Dosage Form	NEXOBRID, for topical gel
Strength/Potency	(b)(4)% gel ((b)(4) g/g)
Route of Administration	Topical
Rx/OTC dispensed	Rx
Indication	Eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns
Applicant/Sponsor	MediWound Ltd. 42 Hayarkon Street, Yavne, Israel 8122745
US agent	Vericel Corporation Michael Halpin 64 Sidney Street, Cambridge, MA 02139 Telephone number: 617-588-5662

Product Overview:

NEXOBRID, is a mixture of proteins extracted from the stems of the pineapple plant (*Ananas comosus* [L.] *Merr.*).

NEXOBRID drug product (DP) is comprised of two components, a sterile lyophilized powder, and a sterile Gel Vehicle for preparation of a gel for topical use. The NEXOBRID DP is lyophilized DS. NEXOBRID DP powder is provided in 50 mL glass vials containing either 2 or 5 g of the lyophilized powder. The Gel Vehicle is provided in 150 mL glass vials containing either 20 or 50 g of the gel. Prior to administration, 2 or 5 g of NEXOBRID DP is mixed with 20 or 50 g Gel Vehicle to produce a (b)(4)% gel for topical application.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Botanical material	Yen-Ming Chan (Botanical Team)	CDER/OPQ/ONDP
Drug Substance (DS)	Leopold Kong	CDER/OPQ/OBP/DBRR IV
Drug Product (DP)		
Immunogenicity assays		
Labeling	CAPT Vicky Borders-Hemphill	CDER/OPQ/OBP
Microbiology and Facilities	Lindsey Brown (DS) Wendy Tan (DP)	CDER/OPQ/OPMA/DBM
Team Leads	LCDR Leslie A. Rivera Rosado (Product Quality) Candace Gomez-Broughton (Micro) Zhong Li (Facilities) Charles Wu (Botanical Team)	CDER/OPQ/OBP/DBRR IV CDER/OPQ/OPMA CDER/OPQ/OPMA/DBM CDER/OPQ/ONDP
Application Technical Lead	LCDR Leslie A. Rivera Rosado	CDER/OPQ/OBP/DBRR IV
Regulatory Business Project Manager	Anita Brown	CDER/OPQ/OPRO

Multidisciplinary Assessment Team:

RPM/TL Assigned:	Jennifer Harmon/Barbara Gould
DDD Director	Kendall A. Marcus
Clinical:	Brenda Carr (MO)/Snezana Trajkovic (TL)
Non-Clinical	Jianyong Wang/Barbara Hill
ClinPharm	Liping (Cindy) Pan/Chinmay Shukla
Biostatistics	Kathleen Fritsch/Mohamed Alosh

1. Names:

a. Proprietary Name: NEXOBRID
b. Trade Name: NEXOBRID
c. Non-Proprietary Name/USAN: N/A (USAN names are not assigned to mixtures)
d. CAS Name: CAS RN 68917-26-0
e. Common Name: "Concentrate of proteolytic enzymes enriched in Bromelain"
f. INN Name: INN cannot be assigned to a heterogeneous mixture of proteolytic enzymes.
g. Compendial Name: N/A
h. OBP systematic name[1]: PROT P80884 (ANAN_ANACO) & PROT Q9S8M1(Q9S8M1_ANACO) & PROT O23791 (BROM1_ANACO) & PROT P14518 (BROM2_ANACO) [MEDIWOUND]

Nomenclature used throughout the dossier

Nomenclature Used	Description
Drug Substance	
Concentrate of proteolytic enzymes enriched in Bromelain	Common name (proposed)
NEXOBRID Drug Substance	Internal code used throughout dossier
Starting Material	
Pineapple Plant stems	*Ananas comosus* [L.] Merr. botanical raw material
Bromelain Special Production (Bromelain SP)	Bromelain SP is extracted from pineapple stems and is used as the intermediate Drug substance

Classification of the Pineapple Plant

Order	Bromeliales
Family	'Bromoeliaceae
Genus	Ananas P. Mill
Species	*Ananas comosus* [L.] Merr.

[1] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

Submissions Assessed:

Submission(s) Reviewed	Document Date	Review Completed (Yes/No)
BLA 761192/1 (Original Submission)	06/29/2020	Yes
BLA 761192/2 (Quality Response to Information Request)	07/31/2020	Yes
BLA 761192/3 (Quality Response to Information Request)	08/13/2020	Yes
BLA 761192/4 (Quality Response to Information Request)	08/26/2020	Yes
BLA 761192/9 (Draft Labeling)	10/02/2020	Yes
BLA 761192/17 (Quality Response to Information Request)	1/25/2021	Yes
STN 761192/21- BLA sections updated with the information presented in sequence 0017	2/17/2021	Yes

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. Drug Master Files (DMF)

DMF #	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed	Comments
(b) (4)			3	N/A	N/A	
			2	Adequate	11/24/2018 05/03/2019 06/19/2020	(b) (4)

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be assessed).

B. Other documents

Document	Application Number	Description
IND	65448	IND submitted to the U.S. Food and Drug Administration (FDA) by MediWound Ltd for NEXOBRID (formerly Debrase®) on 30 July, 2002
Orphan Drug Designation	65448	A letter from the Office of Orphan Products Development was received on 20 August 2003 granting Orphan Drug Designation for NEXOBRID (Orphan Designation No. 02 1561, FDA letter 20 August 2003).
Pre-BLA meeting	65448	pre-BLA meeting regarding the NEXOBRID BLA that occurred between MediWound and FDA on 29 July, 2019 (meeting minutes dated 28 August, 2019).

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:

The Applicant claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with both 21 CFR 25.31(c). The Applicant states that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. *The claim of categorical exclusion is deemed acceptable.*

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of STN 761192 for NEXOBRID manufactured by MediWound, Ltd. The data submitted in this application are not sufficient to support a conclusion that the manufacture of NEXOBRID is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a product quality standpoint, OPQ is recommending a Complete Response letter be issued to MediWound, Ltd. to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues:

Botanical Raw Material

1. Botanical raw material authentication is solely based on morphology. 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, the method validations will not be submitted to the Agency until May 31, 2021; therefore, this continues to be a deficiency.

BSP and Drug Substance 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 bromelain special product (BSP) and drug substance (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)

(b) (4)

4. (b) (4)

5.

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. (b) (4) (b) (4) 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 (b) (4) Provide bioburden limits of the in-process bulk DS (b) (4)

10. We acknowledge the endotoxin test method qualification data for the (b) (4) that was provided on January 25, 2021. However, (b) (4) will not be submitted to the Agency until April 30, 2021; therefore, this continues to be a deficiency.

11. The method suitability for bioburden release testing for DS did not meet acceptance criteria for (b) (4) 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. (b) (4)

15.

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-CMC

20. In your January 25, 2021 response to the information request sent on December 21, 2020, you commit to provide the following data:

    - Data results of BSP, DS, and DP process validation executed according to the protocols submitted with your January 25, 2021 response
    - (b) (4) study and a toxicological assessment
    - Extractable study on the DP and GV rubber stoppers
    - Elemental analysis by ICP-MS on the DP and the gel vehicle (GV) in their final container closure system
    - In-use stability study performed on batches manufactured using the proposed commercial manufacturing process

    To date, these data have not been submitted; therefore, 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). 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. The BLA states that (b) (4) (b) (4) (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 [redacted] method TP-0001. Regarding the validation of TP-0001,
    a. The [redacted] is a critical reagent for this assay. Provide data supporting the robustness of the assay against variability in the [redacted].
    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 (b) (4) (b) (4) 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 (b) (4) 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 (b) (4). Regarding this observation:
        i. Further confirm the identity of these spots, considering that (b) (4) have high degree of similarity
        ii. Provide a justification why there appears to be more fruit bromelain than stem (b) (4) in your DP considering that the botanical raw materials is pineapple stem.
        iii. Considering that (b) (4) has different properties compared to (b) (4) (b) (4) and considering that the (b) (4) provide an assessment of how the current control strategy is adequate and sufficient to ensure lot-to-lot consistency (b) (4)
    b. The cIEF analysis indicates that the samples from the RP-HPLC groups (b) (4) (b) (4) . Provide additional data to fully characterize 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] provide 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 [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]

Facilities

39. 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.

40. 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.

Additional Comments to be Addressed in the Resubmission:

Botanical Raw Materials

1. 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 at the BRM. Therefore, we recommend for future manufacturing, 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.

2. 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: [redacted], [redacted] are included in the pesticides test in USP <561>. [redacted] 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.

3. 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 batch of BSP and drug product.

4. We acknowledge you provided a "List of farmers provided [redacted] 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.

5. 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.

6. 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 [redacted] pineapple stems (GP05)
    e. Identification Method of Stem Cultivar by Characteristics ([redacted] stem sample [redacted] (RS-20)
    f. SOP for appearance assay of pineapple stems ([redacted] stem vs. [redacted] specimen)

BSP and DS- Microbiology

7. Area classification where routine BSP manufacturing processes are conducted have not been provided. Update the description of the BSP manufacturing process to include the area classifications for each process step.

8. Shipping validation data to support routine shipping of the BSP was provided in 3.2.S.2.5. In 3.2.S.2.2, update the description of the BSP shipping procedures to include the maximum shipping duration as validated by the shipping data provided in 3.2.S.2.5.

9. You state that the (b) (4)

(b) (4)

10.

CMC

11. (b) (4)

12.

13.

14. (b) (4)

15.

16 (b) (4)

17. Sections S.4.4 and P.5.4 provides for batch release data for (b) (4) DS batches manufactured between (b) (4) and (b) (4) DP batches, including the 6 registration batches. Provide batch release data and batch genealogy information for all DS and DP batches used in the pivotal clinical trials and those intended for commercial use.

18. (b) (4)

19.

20. Tables 70 through 77 in section P.8.3 Stability Data report RP-HPLC results as total peak area, and not as %RPA. Revise Tables 70-77 to report %RPA in order to facilitate comparison with data from other stability studies reported in this section.

21 (b) (4)

(b) (4)

22. You provided executed batch record for two DP batches manufactured in 2017. However, the manufacturing process in 2017 is not fully reflective of the proposed commercial manufacturing process. The BLA also did not include executed batch records for the BSP or the DS manufacture. Submit executed batch records for BSP, DS, and DP batches that were manufactured using the proposed commercial manufacturing processes.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy
Purity by SEC-UPLC (Purity and identification)	Bioactivity (efficacy), immunogenicity, and safety	Botanical Raw material (BRM), manufacturing process	(b) (4)
Purity by RP-HPLC (Purity)	Bioactivity (efficacy), immunogenicity, and safety	Intrinsic to the protein mixture, raw material, and manufacturing process	
Biological Activity (Potency)	Bioactivity (efficacy) and safety	Raw material, Manufacturing Process, and Storage	

B. Drug Substance Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy
Appearance (Color/ Clarity)	Safety	Intrinsic to the product	(b) (4)
Protein concentration (Content)	Bioactivity (efficacy) and safety	Raw material, Manufacturing process	
pH	Bioactivity and stability	Manufacturing Process and formulation	
Total viable aerobic count (Microbial Control)	Safety, Purity	Raw material, Manufacturing Process	
Test for specific microorganism (Microbial Control)	Safety, Purity	Raw material, Manufacturing Process	
Endotoxin	Safety, Purity	Raw material, Manufacturing Process	
(b) (4) (Microbial Control)	Safety, Purity	Raw material, Manufacturing Process	
(b) (4) (Viral Control)	Safety, Purity	Raw material, Manufacturing Process	
(b) (4) (Impurity)	Potential impact to safety	Raw material, Manufacturing Process	
(b) (4) (Impurity)	Potential impact to safety	Raw material, Manufacturing Process	

CQA (type)	Risk	Origin	Control Strategy
(b) (4) (Impurity)	Potential impact to safety	Raw material, Manufacturing Process	(b) (4)
(b) (4) (Impurity)	Potential impact to safety	Raw material, Manufacturing Process	
Water content	High water content may cause protein degradation during storage can affect the efficacy and safety.	Lyophilization process	

- **Description**:
  Bromelain Special Production (BSP) is an extract obtained from pineapple stems (*Ananas comosus* [L.] *Merr.*) through (b) (4), filtration and lyophilization. Further processing of BSP yields NEXOBRID drug substance (DS). NEXOBRID DS comprises a partially purified mixture of botanical proteins (proteolytic enzymes) extracted from the stems of the pineapple plant.
  The DS is primarily composed of proteins (80-95%), saccharides (b) (4) [buffer components (b) (4) acetic acid, (b) (4) ammonium sulfate), small molecule metabolites (b) (4)
  The primary protein components identified by characterization of the DS and available literature are summarized below. (b) (4)

Protein Component	Characteristics
Stem Bromelain (b) (4)	(b) (4)
Ananain (b) (4)	
Jacalin-like Lectin	

Protein Component	Characteristics
Bromelain Inhibitors	(b) (4)
Phytocystatin	
(b) (4)	

- **Mechanism of Action (MoA):** NEXOBRID is intended to debride burn eschars. The primary component of burn eschars is denatured collagen or "gelatin". NEXOBRID has proteolytic activity against collagens type I and IV, and higher activity against gelatin. The Applicant emphasizes that this difference in activity is clinically relevant since burn eschar is primarily composed of "gelatin".

- **Potency Assays:** Monitoring of NEXOBRID proteolytic activity is performed via a combination of *in vitro* assays: (a) (b) (4) (b) (4) These assays are performed on the DP due to the instability of the DS.

(b) (4)

- **Reference Materials:** Refer to Drug Product Reference Standard section below.

- (b) (4)

- **Manufacturing process summary:**

(b) (4)

- **Container closure:**

(b) (4)

- **Dating period and storage conditions:**

(b) (4)

C. Drug Product [NEXOBRID] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	CQA	Risk	Origin	Control Strategy (b) (4)
Identification	FT-IR UV Spectrum	Control of batch-to-batch variability, efficacy/safety	Botanical raw material (BRM), intrinsic to the protein mixture	
Activity/potency	Potency: Gelatinase Assay Biological activity: Caseinase Activity, Amidolytic Activity	Variability in proteolytic activity will affect the efficacy and safety of the product.	Intrinsic to the protein mixture, raw material, Manufacturing process, storage/stability	
Purity Profile (Product-related variants/impurities)	SEC-HPLC RP-HPLC cIEF	Potential impact to efficacy, Immunogenicity, and Safety.	Intrinsic to the protein mixture, BRM, production process (including lyophilization process), storage	
Assay	Protein Content	Assay assures the strength of the formulation, directly linked to safety and efficacy.	BRM, manufacturing process	
Excipient testing	Acetic Acid	Efficacy	Formulation	
Sterility	Sterile	Presence of microorganisms may affect the safety and integrity of the product.	Manufacturing process, raw materials, filtration steps and environment during powder filling	
Content Composition	Water content	High water content may cause protein degradation during shelf life which can affect the efficacy and safety.	Lyophilization process and powder filling Storage	
Impurities	(b) (4)	Safety	Manufacturing process	
Potential Contaminants		Safety	BRM, raw materials	

CQA (type)	CQA	Risk	Origin	Control Strategy
	(b) (4)			
		Safety	BRM	
		Safety	BRM	

Gel Vehicle

CQA	Risk	Origin	Control Strategy
Appearance	Efficacy	Formulation	(b) (4)
pH			
Homogeneity			
Viscosity			

- **Potency and Strength:** 2 g or 5 g NEXOBRID lyophilized powder in a vial.

- **Summary of Product Design:** NEXOBRID will be supplied as a 50 mL glass vial containing 2 or 5 g of a lyophilized NEXOBRID DP powder together with a 150 mL glass jar containing 20 or 50 mL of a Gel Vehicle, respectively, intended for mixing the powder before administration. One vial of NEXOBRID DP and 1 jar of Gel Vehicle of the corresponding size are supplied together in a cardboard carton kit. After mixing, both dose-size presentations contain the same concentration (b) (4) of active substance.

- **List of Excipients:**

Composition of NEXOBRID Product[a]

Component	Concentration	Content in 2 g Presentation	Content in 5 g Presentation	Grade	Function
NEXOBRID powder	(b) (4) mg/mL[b]	(b) (4) mg	(b) (4) mg	In-house	Active Substance
Acetic acid	(b) (4) mg/mL			USP	Drug substance buffer
Ammonium Sulfate	(b) (4) mg/mL			NF	Drug substance buffe (b) (4)
(b) (4)					

Composition of Gel Vehicle

Component	% (w/w)	Content in 20 g Presentation	Content in 50 g Presentation	Grade	Function
Carbomer 980	(b) (4)			NF	(b) (4)

Disodium (b) (4) phosphate, (b) (4) s	(b) (4)	USP	(b) (4)
Sodium hydroxide		NF	
Water for injection		USP	

NF = National Formulary, q.s. = Quantum sufficit (a sufficient quantity), USP = United States Pharmacopeia

- **Reference Materials:**

(b) (4)

- **Manufacturing process summary:**

(b) (4)

- **Container closure:**
The container for NEXOBRID DP is a 50 mL, Type (b) (4) glass vial (b) (4) stoppered with a (b) (4) stopper and further sealed with an aluminum cap.

The container for the Gel Vehicle is a 150 mL, Type (b) (4) glass jar (b) (4) stoppered with a (b) (4) rubber stopper and further sealed with a (b) (4) cap.

- **Dating period and storage conditions:** The proposed shelf-life is 36 months at 5°C±3°C.

- **List of co-package components, if applicable:** Gel Vehicle in a 150 mL jar.

D. Novel Approaches/Precedents:

First botanical-derived biologic product submitted to CDER for licensure.

E. Any Special Product Quality Labeling Recommendations:

a. Store at 2 - 8°C protected from light.
b. Once the lyophilized powder and the gel vehicle are mixed, the product should be used within 15 minutes.

F. Establishment Information:

Function	Site Information	FEI Number	Preliminary Assessment	Final Recommendation
Manufacturing, filling, packaging, labelling, and all quality control testing of Bromelain SP intermediate drug substance (BSP)	**Challenge Bioproducts Company Ltd** 17, Tou-Kong 12 Road Tou-Liu Industrial Park Tou-Liu City, Yun-lin Hsien Taiwan.	3004282026	No Inspection history	PLI Deferred Travel Restrictions-COVID-19
Release testing of BSP. Manufacture, filling, packaging, labeling, and quality control testing (including both release and stability) of NexoBrid DS, DP, and Gel Vehicle.	**MediWound Ltd** 42 Hayarkon St., Yavne 8122745 Israel	3003889199	No Inspection history	PLI Deferred Travel Restrictions-COVID-19
(b) (4)				Approved
				Approved

(b) (4)

Approved

Facilities:

An inspection of the **Mediwound Ltd.** (FEI 3003889199), Yaven, Israel facility and an inspection of the **Challenge Bioproducts Co., Ltd.** (FEI 3004282026), Tou-Liu City, Taiwan facility are required before the 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 this application. The Applicant 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 this application.

G. Lifecycle Knowledge Management:

c. Drug Substance and Drug Product:

i. Protocols approved:
None

ii. Outstanding assessment issues/residual risk:
Refer to comments to the applicant to be send with the Complete Response Letter

iii. Future inspection points to consider:
Refer to comments to the applicant to be send with the Complete Response Letter

Leslie
Rivera-Rosado

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BOTANICAL BIOLOGICS LICENSE APPLICATION PRIMARY REVIEW

BY

BOTANICAL REVIEW TEAM

Application Type:	BLA 351(a)
BLA Number:	761192
Stamp Date:	6/29/2020
Applicant:	MediWound Ltd.
Product Name:	NexoBrid (concentrate of proteolytic enzymes enriched in Bromelain)
Brand Name:	NexoBrid
PDUFA Date:	6/29/2021
Dosage Form:	Gel (2 or 5 g of a lyophilized NexoBrid Drug Product powder in 20 or 50 (b) (4) of a Gel Vehicle)
Route of Administration:	Topical
Botanical Raw Material:	(b) (4) stems of pineapple (*Ananas comosus* [L.] Merr.)
Botanical Drug Substance:	Concentrate of proteolytic enzymes enriched in Bromelain
Indication Requested:	Eschar removal (debridement) in adults with deep partial thickness and/or full thickness thermal burns
Botanical Review Team Reviewer:	Yen-Ming Chan, Ph.D.
Review Completion Date:	3/29/2021
Botanical Review Team Leader:	Charles Wu, Ph.D.
Office of New Drug Review Division:	Division of Dermatology and Dentistry

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Yen-Ming Chan

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Charles Wu

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Comments: The primary botanical review is well conducted. I concur with all comments and recommendations included in the review.

BLA STN 761192

NEXOBRID

(“*concentrate of proteolytic enzymes enriched in Bromelain*”)

MediWound, Ltd.

Leopold Kong, Ph.D., Chemist
Leslie A. Rivera Rosado, Ph.D., Team Lead
Christopher Downey, Ph.D., Review Chief

Division of Biotechnology Review and Research IV

OBP CMC Review Data Sheet

1. BLA#: STN 761192 (docuBridge Link)

2. REVIEW DATE: March 11, 2021

3. PRIMARY REVIEW TEAM:

Discipline	Reviewer	Branch/Division
Botanical Raw Material	Yen-Ming Chan (Botanical Team)	CDER/OPQ/ONDP
Drug Substance Intermediate (Bromelain Special Production)	Leopold Kong	CDER/OPQ/OBP/DBRR IV
Drug Substance (DS)	Leopold Kong	CDER/OPQ/OBP/DBRR IV
Drug Product (DP)		
Immunogenicity assays		
OBP Labeling	Vicky Borders-Hemphill	CDER/OPQ/OBP
Micro/Facility DS	Lindsey Brown	CDER/OPQ/OPMA/DBM/BMB1
Micro/Facility DP	Wendy Tan	CDER/OPQ/OPMA/DBM/BMB1
Team Leads	LCDR Leslie A. Rivera Rosado (Product Quality) Zhong Li (OPMA Facilities) Candace Gomez-Broughton (OPMA Micro) Charles Wu (Botanical)	CDER/OPQ/OBP/DBRR IV CDER/OPQ/OPMA/DBM/BMB1 CDER/OPQ/OPMA/DBM/BMB1 CDER/OPQ/ONDP
Application Team Lead	LCDR Leslie A. Rivera Rosado	CDER/OPQ/OBP/DBRR IV
Regulatory Business Project Manager	Anita Brown	CDER/OPQ/OPRO
RPM	Jennifer Harmon/Barbara Gould	CDER/OND/ORO/DROII
Cross-disciplinary Team Lead	Snezana Trajkovic	CDER/OND/OII/DDD
Medical Officer	Brenda Carr (MO)/Snezana Trajkovic (TL)	CDER/OND/OII/DDD
Pharm/Tox	Jianyong Wang/Barbara Hill	CDER/OII/DPT-II
Clinical Pharmacology	Liping (Cindy) Pan/Chinmay Shukla	CDER/OTS/OCP/DIIP
Statistics	Kathleen Fritsch/Mohamed Alosh	CDER/OTS/OB/DBIII
Division Signatory	Kendall Marcus	CDER/OND/OII/DDD
Office Signatory	Julie G. Beitz	CDER/OND/OII

4. MAJOR GRMP DEADLINES

Filing Meeting: August 14, 2020
Mid-Cycle Meeting: December 1, 2020 (internal) & December 14, 2020 (w/ applicant)
Primary Review Due: ODD: March 30, 2021 & ODD: April 5, 2021
Late-Cycle Meeting: February 26, 2021 (internal) & March 24, 2021 (w/ applicant)
PDUFA Action Date: June 29, 2021

5. COMMUNICATIONS WITH APPLICANT AND OND:

Communication/Document	Date
Kickoff Meeting	8/12/2020
Internal meeting: Filing	8/14/2020
Internal meeting: Mid-cycle	12/01/2020
Mid-cycle communication with applicant	12/14/2020
Internal meetings: Labeling	1/7/2021
Internal meeting to discuss BARDA's question of whether the applicant's plan would "likely qualify as a major amendment allowing 90-day PDUFA extension?"	1/22/2021
Internal meetings: Labeling	2/12/2021
Internal meeting to discuss Product Quality approvability issues	2/16/2021
Internal meeting: Late-cycle	2/26/2021

6. SUBMISSION(S) REVIEWED:

Submission(s) Reviewed	Document Date	Review Completed (Yes/No)
STN 761192/1- BLA Original Application	6/29/2020	Yes
STN 761192/2- Response to IR dated 7/7/2020 (Manufacturing Schedules)	7/31/2020	Yes
STN 761192/3- Response to IR dated 8/11/2020	8/13/2020	Yes
STN 761192/4- Response to IR dated 8/20/2020 (DMF Letters)	8/26/2020	Yes
STN 761192/17- Response to IR dated 12/21/2020	1/25/2021	Yes
STN 761192/21- BLA sections updated with the information presented in sequence 0017	2/17/2021	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NexoBrid
USAN/ INN: N/A (*USAN or INN names are not assigned to mixtures*)
Non-Proprietary: MediWound proposes the non-proprietary name (b) (4)
CAS name: CAS RN (68917-26-0)
Common name: Concentrate of proteolytic enzymes enriched in Bromelain
OBP systematic name[1]: PROT P80884 (ANAN_ANACO) & PROT Q9S8M1(Q9S8M1_ANACO) & PROT O23791 (BROM1_ANACO) & PROT P14518 (BROM2_ANACO) [MEDIWOUND]

8. PHARMACOLOGICAL CATEGORY: Proteolytic enzymes

9. DOSAGE FORM: For topical gel

10. STRENGTH/POTENCY:

(i) NexoBrid Drug Product is comprised of two components:

- 50 mL type (b) (4) glass vial containing 2 or 5 g sterile lyophilized NexoBrid powder

[1] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

- 150 mL type [redacted] glass bottle containing 20 or 50 g sterile Gel Vehicle

Prior to administration, the NexoBrid powder is mixed with the Gel Vehicle to produce a [redacted]% gel ([redacted] g/g).

(ii) Type of potency assay (s):

- Potency by [redacted] *in vitro* enzymatic activity assay
- Potency by [redacted] *in vitro* enzymatic activity assay
- Potency by [redacted] *in vitro* enzymatic activity assay

11. ROUTE OF ADMINISTRATION: Topical

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Authorization	COMMENTS (STATUS)
[redacted]			1.4.1	Current
			1.4.1	Current

13. INSPECTIONAL ACTIVITIES

An inspection of the **Mediwound Ltd.** (FEI 3003889199), Yaven, Israel facility and an inspection of the **Challenge Bioproducts Co., Ltd.** (FEI 3004282026), Tou-Liu City, Taiwan facility are required before the 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 may be unable to conduct an inspection of the Mediwound Ltd. Facility or an inspection of the Challenge Bioproducts Co., Ltd. facility prior to the User Fee Date.

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.

[redacted] is responsible for testing specified microorganisms in NexoBrid Drug Substance [redacted] in the BSP. **Final facility recommendation: Acceptable/ Approval**

14. CONSULTS REQUESTED BY OBP: None

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS

First botanically-derived biological product submitted to the Agency for licensing.

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Christopher Downey, Ph.D. Review Chief Division of Biotechnology Review and Research IV (DBRR IV) Office of Biotechnology Products (OBP) Office of Pharmaceutical Quality (OPQ)	See attached
LCDR Leslie Ann Rivera Rosado Product Quality Team Leader DBRR IV, OBP, OPQ	See attached
Leopold Kong, Ph.D. Product Quality Assessor DBRR IV, OBP, OPQ	See attached

B. CC Block

Recipient	Date
Jennifer Harmon/Barbara Gould Clinical Division BLA RPM	
OBP/DBRR IV/File/BLA STN 761192	

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Christopher Downey

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Leslie Rivera-Rosado

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Leopold Kong

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