CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218808Orig1s000, 218820Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 218808
Assessment # 1

Drug Product Name	CRENESSITY (Crinecerfont)
Dosage Form	Capsule
Strength	25 mg, 50 mg, 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Neurocrine Biosciences Inc.
US agent, if applicable	N/A
Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	N/A
Maximum Daily Dose	200 mg/day
Alternative Methods of Administration	None

Submission(s) Assessed (eCTD Sequence)	Document Date	Discipline(s) Affected
0001	04/29/2024	Quality (Original NDA submission)
0005	06/14/2024	Quality
0006	06/18/2024	Quality
0009	07/08/2024	Quality
0010	07/16/2024	Quality
0013	08/26/2024	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Stephanie Springer	Zhengfu Wang
Drug Product	George Ward	Akm Khairuzzaman
Manufacturing	Kejun Cheng	Aditi Thakur
Biopharmaceutics	Rajesh Savkur	Haritha Mandula
Environmental	George Ward	Akm Khairuzzaman
Regulatory Business Process Manager	Oluwafunmike Ajomale	
Application Technical Lead	Akm Khairuzzaman	

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. **DMFs:** Acceptable.

DMF No.	Type	Holder	Item Referenced	Status	Comments
(b) (4)	IV		(b) (4)	Active	Adequate
	III			Active	Adequate
	III			Active	Adequate
	III			Active	Adequate

B. OTHER DOCUMENTS: ***IND, RLD, RS, Approved NDA***

None

2. CONSULTS The Office of Pharmaceutical Quality Research (OPQR), OPQ was consulted for analytical method verification.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 218808 is recommended for **approval**. As part of this action, an expiration period of 15 months for the product, stored at 15°C - 25°C (59° F to 77° F) in the commercial packaging, is granted.

II. SUMMARY OF QUALITY ASSESSMENTS

In accordance with section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, the applicant Neurocrine Biosciences Inc., submitted NDA 218808 to seek marketing approval for CRENESSITY™ (crinecerfont) capsule, for oral use. Crinecerfont is a new chemical entity (NME). Its identity, purity, impurity, and manufacturing are adequately controlled through appropriate quality management system and validated analytical methods. The drug substance is stable for the intended storage period in its commercial packaging system. The new drug product is an oral soft gel capsule formulated with excipients such as: medium-chain triglycerides, propylene glycol dicaprylate/ dicaprate , lauroyl polyoxyl-32 glycerides, and vitamin E polyethylene glycol succinate. Note that propylene glycol dicaprylate has not been used in any oral products before but its quantitative level used in the formulation is found to be acceptable by the Pharm/tox reviewer. The drug product is supplied in three different strengths (25 mg, 50 mg and 100 mg), packed in a HDPE bottle with child resistant cap. The manufacturing process is adequately controlled by the quality management system of the listed cGMP compliant manufacturing facilities. From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, potency, and stability.

A. Quality Assessment Overview

Drug Substance: Adequate

Crinecerfont, a new synthetic small molecule that has one stereocenter in the S configuration. Sufficient characterization is provided to assure the identity and purity of the drug substance. The drug substance structure has been characterized adequately using ^{1}H NMR, ^{13}C NMR, elemental analysis, FTIR, MS, and single crystal X-ray structure determination. Absolute configuration of the stereocenter is confirmed by X-ray crystal structure. The commercial manufacturing process yields the drug substance as a single polymorph (b) (4) The drug substance is BCS Class 4. However, particle size and polymorphism of the drug substance are not critical (b) (4)

(b) (4) The applicant has used the well-established synthesis for manufacture of the drug substance which adequately controls residual solvents, elemental impurities, and mutagenic impurities as per the applicable ICH guidance. Starting materials are appropriately designated. The drug substance quality control specification includes relevant quality attributes such as description, identification by FTIR and HPLC, assay, chiral purity, water content, organic impurities, and microbial limits. Analytical methods to control the quality of the drug substance are adequate and appropriately validated. Stability data support the proposed re-testing period of (b) (4) months when stored (b) (4) For additional information, please refer to Dr. Stephanie Springer's review in Panorama dated 08/8/2024.

Drug Product: Adequate

Crinecerfont capsule is formulated with excipients such as: medium-chain triglycerides (b) (4) propylene glygcol dicaprylate/dicaprate (b) (4) lauroyl polyoxyl-32 glycerides (b) (4) and vitamin E polyethylene glycol succinate (b) (4) (b) (4) (b) (4) The quantitative level of the novel excipient (i.e., propylene glycol dicaprylate) in the formulation is found to be adequate from pharm/tox as well as from CMC perspective. There are (b) (4) in the product formulation and there is no change in the formulation composition between the commercial product and the Phase 3 trial product. (b) (4) particle size of the drug substance is not expected to impact the product quality. During the product development, critical quality attributes were identified, and they are adequately controlled by product specification which includes tests for description, identification, assay, degradation products, dissolution, uniformity of dosage units, and microbial attributes. All analytical methods for quality control of the product are adequate and they are appropriately validated. Based on the provided stability data, the Applicant's proposed shelf-life of 15 months is acceptable when stored at 15°C - 25°C (59° F to 77° F). However, Dr. Ward's review mentions tha (b) (4) The drug product is supplied in a 120cc HDPE bottle with a 38mm child resistant cap and foil seal over the bottle opening. For additional information, please refer to Dr. George Ward's review in Panorama dated 10/07/2024.

Labeling: Adequate

Updated labeling information is found to be adequate by the chemistry reviewer, Dr. George Ward. Minor edits were made in the chemistry section of the package insert.

Manufacturing: Adequate

The drug product is manufactured (b) (4) The batch size for the is (b) (4) The manufacturing process reviewer, Dr. Kejun Cheng concludes that the manufacturing process is adequately controlled by appropriate control strategy, including in-process controls.

Biopharmaceutics: Adequate

The biopharmaceutics reviewer, Dr. Rajesh Savkur concludes that crinecerfont, a poorly soluble drug, (b) (4) For quality control purpose, the Applicant's proposed two-tier dissolution method is found to be adequate, and the overall biopharmaceutics risk is low. Dr. Savkur also concludes that the capsule fill formulation of the three strengths is compositionally proportional to each other. Based on the totality of the information and data submitted in support of the bridging across the formulations, additional strengths, manufacturing sites and batch sizes, a waiver for demonstration of in vivo bioequivalence for the 25 mg and 50 mg strengths of the "to be marketed" formulation is found to be acceptable as per the 21 CFR 320.22(d)(2). No additional in vivo study is required.

Manufacturing Facilities: Adequate

Based on the inspection history, manufacturing experience and acceptable compliant status, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended an overall approval for all the currently listed manufacturing and testing facilities concerning this NDA.

B. Risk Assessment: Overall quality risk is low.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Assay (API), stability	Medium to Low	(b) (4)	Low	(b) (4)
Physical stability (solid state)	Low		Low	
Degradation impurities	Medium to low		Low	
Dissolution	Medium to Low		Low	
Microbial limits	Low		Low	
Content uniformity	Low		Low	

C. List of Deficiencies for Complete Response:

None

Application Technical Lead Name and Date:

Akm Khairuzzaman, Ph.D. 10/07/2024

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CHAPTER IV: LABELING

NDA Number	NDA 218808
Assessment Cycle Number	#1
Drug Product Name	CRENESSITY / Crinecerfont soft gel capsule

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**0001**
Patient Information	Adequate	**0001**
Instruction for Use (IFU)	Adequate	**0001**
Container Labels	Adequate	**0001**
Carton Labeling	Adequate	**0001**

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001, 1	4/29/2024	Initial NDA Package

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	The proposed name, CRENESSITY® (crinecerfont) capsules, for oral use is adequate.
Route(s) of administration	Adequate	Route of administration is in the title.
Controlled drug substance symbol (if applicable)	N/A	Not a controlled drug substance.
Initial U.S. Approval [§201.57(a)(3)]	Adequate	Adequate.
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Dosage form: Capsules Strength: 25, 50, and 100 mg

[2] Draft guidance: *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)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).
[4] Draft guidance: *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); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	Not a salt.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	Not a tablet.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	Not an injectable product.

Assessment: *Adequate*

The highlights of prescribing information is acceptable from Drug Product's perspective.

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *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 <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	No special instructions for product preparation.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	Administration information is adequate and supported by the product quality information.
For parenteral products: include statement: *"Parenteral drug*	N/A	Not a parenteral product.

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."[11]		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	No USP labeling requirement.
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	Not a radioactive product.
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	Not a hazardous product.

Assessment: *Adequate*

Section 2 is adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

[redacted]

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	The various dosage forms are described in adequate detailed and easily differentiated.
Strength(s) in metric system	Adequate	Dosage form strengths are stated in metric units.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	Not a salt.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	Identifying characteristics are described in adequate detailed.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	Not a tablet.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	Not a parenteral product.

Assessment: *Adequate*

Section 3 is adequate.

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	The proprietary name, CRENESSITY® is adequate.
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Single dose taken orally. This is adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	Not a salt.

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	The inactive ingredients changed to alphabetical list.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Not a parenteral product.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	No alcohol present.
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	Not a sterile product.
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	Crinecerfont: corticotropin-releasing factor 1 antagonist.
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	Chemical name, structure and molecular weight are adequately described.
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	Not a radioactive product.

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	Chemical and physical properties are described in adequate detail.
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	Gluten statement is not necessary.
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Adequate	No misleading or promotional statements.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	No USP labeling requirement.

Assessment: *Adequate*

With the correction to the inactive ingredient list, section 11 is adequate.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

[redacted]

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Each dosage form is described in adequate detail.
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	Strengths are stated in metric system.
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	25 mg and 50 mg: 60 capsules/bottle 100 mg: 30 capsules/bottle
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	Dosage forms are distinct and described clearly.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	Not a tablet.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	Not a parenteral product.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	No special handling instruction.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Storage conditions are described per USP <659> and in line with drug product stability data.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	N/A	Not applicable.
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	Added to section 16.

Assessment: *Adequate*

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Requested to be added by another reviewer.

Assessment: *Adequate*

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	CRENESSITY® is an adequate name.
Special preparation instructions (if applicable).	N/A	No special preparation necessary.
Storage and handling information (if applicable).	Adequate	Store CRENESSITY capsules at room temperature between 15°C to 25°C (59°F to 77°F).

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	No desiccant.
Active ingredient(s) (if applicable).	Adequate	Active ingredient is present
Alphabetical listing of inactive ingredients (if applicable).	Adequate	Not necessary for capsule formulation.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Neurocrine Biosciences, Inc., San Diego, CA 92130, U.S.A.

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(b) (4)

[redacted]

[25] Carton and Container Labeling Resources

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	Name is present.
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	Strength is in metric on all three labels.
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	N/A	Yes	Oral capsule product not required.
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	Not a salt
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	# of capsules stated.
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	"Rx only" is present.
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	Present
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	Present and adequately sized.
Storage conditions. If applicable, include a space on	Adequate	Yes	Storage conditions described properly.

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
the carton labeling for the user to write the beyond-use-date (BUD).			
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Yes	Not a parenteral product.
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Yes	Oral drug product
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	Not a parenteral product.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	No alcohol is present.
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	Present.

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	References package insert for dosage guidance.
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	Neurocrine Biosciences is present.
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	Present.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	No medication guide.
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	Not an injectable product.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	No USP monograph labeling requirement.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]	N/A	Yes	No differences.

[31] USP General Notices 3.20 Indicating Conformance

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
And others if space is available.	N/A	Yes	N/A

Assessment of Carton Labels and Container Labeling: *Adequate*

The container label is adequate.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

None.

Primary Labeling Assessor Name and Date: George Ward, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Akm Khairuzzaman, Ph.D.

Akm Khairuzzaman

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Date: 9/10/2024 11:34:51AM
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George Ward

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Date: 9/10/2024 10:58:31AM
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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-218808-ORIG-1
Submission History	4/29/2024 (Sequence 0001): Original submission 7/8/2024 (Sequence 0009): Response to Information Request – Quality
Drug Product Name/ Strength	CRENESSITY™ – Crinecerfont softgel capsules, 25 mg, 50 mg and 100 mg
Route of Administration	Oral
Applicant Name	Neurocrine Biosciences Inc.
Therapeutic Classification/ OND Division	Division of General Endocrinology (DGE)
Proposed Indication	(b) (4)
IND Number	IND-132849
Primary Reviewer	Rajesh Savkur, Ph.D.
SPQA	Haritha Mandula, Ph.D.
Assessment Recommendation	**Adequate**

EXECUTIVE SUMMARY

In this submission, the Applicant seeks approval of CRENESSITY™ – Crinecerfont softgel capsules, 25 mg, 50 mg and 100 mg. Crinecerfont, a selective corticotropin releasing factor 1 (CRF1) receptor antagonist, has been developed (b) (4) (b) (4) (b) (4) NDA-218808-ORIG-1 was initially submitted to the Division of General Endocrinology (DGE) on 4/29/2024 under section 505(b)(1). The proposed drug product (CRENESSITY – Crinecerfont softgel capsules, 25 mg, 50 mg and 100 mg) comprises of a poorly aqueous soluble active pharmaceutical ingredient (API), crinecerfont, (b) (4) The recommended dosage of the drug product for patients 4 years of age and older is shown below, and should be taken with food, twice daily (in the morning and evening).

Age and Body Weight	Dosage Regimen
Adults (18 and older) Pediatric patients weighing ≥55 kg	100 mg twice daily (200 mg per day)
Pediatric patients weighing 20 kg to <55 kg	50 mg twice daily (100 mg per day)
Pediatric patients weighing 10 kg to <20 kg	25 mg twice daily (50 mg per day)

***Assessment Summary*:**

The Biopharmaceutics assessment focuses on evaluating (i) the *in vitro* dissolution method development, the *in vitro* dissolution data and the *in vitro* dissolution acceptance criterion, (ii) the bridging data between the clinical and commercial/to-be-marketed drug products, the manufacturing sites and batch sizes, and (iii) biowaiver request for the lower strengths of the proposed drug product.

- ***In vitro* dissolution method and acceptance criterion:**

  The proposed drug product contains a low-solubility drug substance and is formulated as a solution using Medium-Chain Triglycerides and Propylene Glycol (b) (4) and Lauroyl Polyoxyl-32 Glyceride and Vitamin E Polyethylene Glycol Succinate (Vitamin E TPGS) (b) (4)

  The Applicant proposed a two-tiered dissolution method (b) (4) The Applicant's proposal to adopt a two-tiered dissolution method with the use of pepsin in the tier 2 medium is found acceptable. The proposed dissolution method possesses limited discriminating ability with respect to changes in the CFVs/CPPs/CMAs (towards a change in the concentration of (b) (4)) and is found acceptable. Based on the totality of the submitted information, (b) (4) to satisfy the specification of "Q= (b) (4)% in 45 minutes" at the S1/S2 stages, the proposed acceptance criterion is found acceptable. The final dissolution method and acceptance criterion as agreed upon by the Applicant and the FDA for QC of Crinecerfont softgel capsules, 25 mg, 50 mg and 100 mg at batch release and through stability is shown below in Table 1.

Table 1: Approved *in vitro* dissolution method and acceptance criterion for Crinecerfont softgel capsules, 25 mg, 50 mg and 100 mg

Approved *in vitro* dissolution method				Approved *in vitro* dissolution acceptance criterion
Source	**Apparatus**	**Medium/ Volume**	**Agitation speed/ Temperature**	
In-house	USP apparatus 1 (20 mesh)	Tier 1: 900 mL of 0.6% SDS in 0.1 N HCl Tier 2: "A" – first 12 min:	Speed: 100 rpm Temp: 37 °C	NLT (b) (4)% (Q) in 45 minutes

		800 mL of 0.1 N HCl + Pepsin, 750,000 U/L "B" – after 12 min: 100 mL of 5.5% SDS in 0.1 N HCl		

From a Biopharmaceutics perspective, based on the identification of the Critical Formulation Variables (CFVs)/Critical Bioavailability Attributes (CBAs), the initial risk is considered to be "Medium". The initial risk is with the assumption that all applicable GMPs are established and maintained for the dispensing unit operation. Based on the risk mitigation and control strategies, the final risk has been updated to "Low" (Table 2).

Table 2: Risk Assessment

Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Medium	• The drug product is an immediate-release product. • (b) (4)	Low	(b) (4) • The in vitro dissolution method and acceptance criterion possess the ability to discriminate and reject the variant batch with a reduced concentration of (b) (4)

- **Product Bridging:**

  Bridging of drug product formulations across product development:

  The soft-gelatin capsule is the final to-be-marketed (TBM) commercial formulation. The TBM drug product is proposed in three (25 mg, 50 mg and 100 mg) strengths. The capsule fill formulation of the three strengths is compositionally proportional to each other. Phase 3 studies were conducted on the 50 mg hard-gelatin capsule. A Phase 1 comparative bioavailability study (S# NBI-74788-1736) was conducted to bridge the 100 mg strength of the TBM product to the Phase 3 50 mg hard-gelatin capsule. Based on the 90% CI values of the PK parameters (C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$) complying with the acceptance criterion range of 0.8–1.25, the 100 mg strength of the TBM product (soft-gelatin capsule) can be considered to be satisfactorily bridged to the 50 mg strength of the Phase 3 clinical hard-gelatin capsule.

  Bridging of additional/lower (25 mg and 50 mg) strengths:

  A Phase 1 study was conducted on the TBM formulation of the 100 mg strength. In accordance with 21 CFR 320.22(d)(2), in support of the bridge between the TBM formulation of the 25 mg and 50 mg strengths and the TBM formulation of the 100 mg strength, the Applicant submitted data demonstrating that –

- Crinecerfont exposure (C_{max} and AUC) parameters following single oral doses of crinecerfont are dose-proportional over a clinically relevant dose range for the capsule formulation (25 to 200 mg).

- The manufacturing process for the fill formulation, and the qualitative and quantitative composition are proportional across the 100 mg, 50 mg and 25 mg strengths of the TBM capsule.

- The reference product (100 mg TBM capsule) used for *in vitro* comparison was demonstrated to be bioequivalent to the Phase 3 capsule in an *in vivo* clinical study.

- Comparative *in vitro* dissolution profile data (*f*2 values) between the TBM 100 mg capsule (1 × 100 mg) and the TBM 25 mg (as 4 × 25 mg and 1 × 25 mg [% label claim]) and 50 mg (as 2 × 50 mg and 1 × 50 mg [% label claim]) registration capsules.

Bridging of manufacturing sites:
A single site (b) (4) has been used to manufacture the TBM batches of the three strengths. Phase 1 studies were conducted on the 100 mg strength of the TBM product. Thus, a bridging of manufacturing sites is not required.

Bridging of batch sizes:
The batch size of the TBM exhibit/clinical batches of the three strengths manufactured at (b) (4) is (b) (4) capsules. Since the range of the sizes of the exhibit/clinical batches are within 10× of each other, bridging of the exhibit/clinical batches based on the Phase 1 studies is found acceptable. The size of the intended commercial batches of the three strengths is (b) (4) capsules. Since the range of the sizes of the exhibit/clinical and intended commercial batches are within a factor of 10 times of each other, based on the SUPAC-IR *Guidance*, an in vitro dissolution profile comparison between exhibit/clinical and intended commercial batches is recommended to bridge the intended commercial batches to the clinical batch.

- **Biowaiver request:**
  Based on the totality of the information submitted in support of the bridging across the formulations, additional strengths, manufacturing sites and batch sizes, the data in support of a waiver for demonstration of *in vivo* bioequivalence for the 25 mg and 50 mg strengths of the TBM formulation in accordance with 21 CFR 320.22(d)(2) is found acceptable. An additional *in vivo* study is not required. The efficacy studies for the 25 mg and 50 mg strengths will be assessed by the Clinical/Clinical Pharmacology Reviewer.

The list of submissions assessed in the NDA are shown below in Table 3.

Table 3: List of Submissions Being Assessed

IND/NDA	eCTD sequence #	Date of submission	Document
NDA	0001	4/29/2024	Original Submission
NDA	0009	7/8/2024	Response to Information Request – Biopharmaceutics #1

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed*):
None

OVERALL BIOPHARMACEUTICS RECOMMENDATION:
From a Biopharmaceutics perspective, NDA-218808-ORIG-1 for CRENESSITY – Crinecerfont softgel capsules, 25 mg, 50 mg and 100 mg, is **adequate** and is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

B.1. BCS DESIGNATION:

Assessment: Not Applicable

Solubility:

The active pharmaceutical ingredient (API), crinecerfont, is a white to light yellow solid that is poorly soluble in water and is highly soluble in organic solvents (Tables 4A and 4B). The solubility of the crinecerfont drug substance across the physiological pH range of 1 to 6.8 is <0.01 mg/mL (Table 4C).

Table 4A: Physicochemical properties of the crinecerfont API

Physical/Chemical Properties	Description
Appearance	White to light yellow solid
Dissociation constant[a]	pKa = 4.11 (calculated)
Partition coefficient[a]	Log P = 7.75 (calculated)
Optical activity (specific rotation)	$[\alpha]_D$: - 186.1° (determined at 20 °C with a 10 mg/mL solution in methanol)
Melting point	Melt endotherm with an onset of 87 °C
Hygroscopicity	Non-hygroscopic
Crystallinity	Crystalline
Polymorphism	(b) (4)
Morphology	Plate-like crystals
Solubility	Solubility data at 25 °C
Biopharmaceutical Classification System (BCS)	Class 4

Table 4B: Solubility data of the crinecerfont API in aqueous and organic solvents

Solvent	Solubility at 25°C (mg/mL)
Acetone	> 531
Acetonitrile	187
t-Butyl methyl ether	340
Dichloromethane	> 814
Ethanol	28
Ethyl acetate	508
n-Heptane	26
Isopropyl alcohol	15
Methanol	25
Tetrahydrofuran	782
Toluene	572
Water	< 0.01
Water (pH 1 – 9)[a]	< 0.01

[a] Solubility measured at 9 points in buffer systems from pH 1 to pH 9. All measurements were < 0.01 mg/ml.

Table 4C: Aqueous solubility data of the crinecerfont API in the pH range of 1.0 to 9.0

Aqueous Media	Solubility (mg/mL)
pH 1.0 USP Buffer	< 0.01
pH 2.0 USP Buffer	< 0.01
pH 3.0 USP Buffer	< 0.01
pH 4.0 USP Buffer	< 0.01
pH 5.0 USP Buffer	< 0.01
pH 6.0 USP Buffer	< 0.01
pH 7.0 USP Buffer	< 0.01
pH 8.0 USP Buffer	< 0.01
pH 9.0 USP Buffer	< 0.01
DI Water (pH 8.5 at saturation)	< 0.01

Permeability:
The apparent permeability (P_{app}) of the API (using [^{14}C]crinecerfont) across Caco-2-TC7 cell monolayers was 2.2×10^{-7} cm/s.

***Reviewer's assessment*:**
At the highest strength of 100 mg and solubility of <0.01 mg/mL, (b) (4) . Thus, the crinecerfont API can be considered as a low-solubility drug substance.

The crinecerfont API exhibits a low apparent permeability (P_{app}) of 2.2×10^{-7} cm/s.

Based on the low-solubility and low-permeability, the Applicant has classified the crinecerfont API as a BCS class 4 compound. Since the Applicant has not requested a formal claim for the BCS designation, the permeability and BCS class of the crinecerfont API have not been assessed.

B.2. IN VITRO DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

Assessment: Adequate

B.2.1. In vitro dissolution method:

During the drug product development stage, dissolution media and volume were established based on the drug substance solubility and the immediate release nature of the dosage form. The dissolution method was tiered to allow the use of a proteolytic enzyme in the event gelatin capsule crosslinking was observed. As part of the dissolution method development, the following dissolution parameters were investigated:

(b) (4)

The details are provided in the dissolution method development report (page 1). The two-tiered dissolution method adopted by the Applicant for QC of the drug product at release and through the stability program is shown below in Table 5:

Table 5: Proposed dissolution method for QC of the drug product

Apparatus	USP apparatus 1 (20 mesh)
Medium/Volume	Tier 1: 900 mL of 0.6% SDS in 0.1 N HCl
	Tier 2: "A" – first 12 min: 800 mL of 0.1 N HCl + Pepsin, 750,000 U/L "B" – after 12 min: 100 mL of 5.5% SDS in 0.1 N HCl
Agitation speed	100 rpm
Temperature	37 °C

***Reviewer's assessment*:**

The proposed drug product contains a low-solubility drug substance and is formulated [redacted] using Medium-Chain Triglycerides and Propylene Glycol [redacted], and Lauroyl Polyoxyl-32 Glyceride and Vitamin E Polyethylene Glycol Succinate [redacted]

This Reviewer notes that the Applicant proposed a two-tiered dissolution method [redacted] The tier 2 dissolution is conducted in two stages:

- Stage "A" – First 12 minutes – containing 800 mL of 0.1 N HCl + 750,000 U/L Pepsin: In the response to IR#1 Item#2 (Appendix 2), [redacted]

- Stage "B" – After 12 minutes – addition of 100 mL of 0.1 N HCl containing 5.5% SDS: In accordance with the proposed tier 1 dissolution medium (900 mL of 0.1 N HCl + 0.6% SDS), SDS was added to the Stage "B" medium (b) (4) . The addition of 100 mL of 0.1 N HCl containing 5.5% SDS would result in a final concentration of 0.6% SDS in the 900 mL 0.1 N HCl medium.

In accordance with USP <711>, the Applicant's proposal to adopt a two-tiered dissolution method by adding Pepsin (at a concentration of 750,000 U/L in the dissolution medium with a pH ≤4.0) in the tier 2 medium is found acceptable.

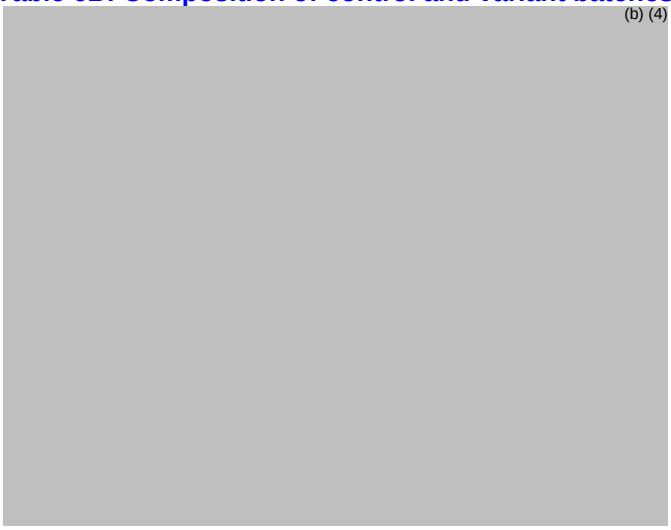
Discriminating ability of the proposed method: The Critical Formulation Variables (CFVs) and the Critical Processing Parameters (CPPs) that could impact the bioavailability of the drug product and hence be putative Critical Bioavailability Attributes (CBAs) are show below in Table 6A. The composition of the control and variant batches of the 100 mg strength – with aberrations in the putative CBAs – that were evaluated for the discriminating ability of the method is shown below in Table 6B.

Table 6A: CFVs and CPPs evaluated for discriminating ability of the dissolution method

Type	Description	Variation	Strength	Lot Number	DS Lot Number (site)
Critical Formulation Variables (CFV)	(b) (4)		100 mg	23MC-95	20796913
			100 mg	23MC-94	20796913
Processing Parameters			100 mg	23MC-93	20796913
			100 mg	5641729A	20796913

Table 6B: Composition of control and variant batches

(b) (4)



The mean dissolution data of the biobatch (BioB# 4917947) and the variant batches (B#s 23MC-93, 23MC-94, 23MC-95 and 5641729A) are shown below in Table 6C:

Table 6C: Mean dissolution data of the control and variant batches

Specification / Batch information	% dissolved (min) 5 —	10 —	15 —	20 —	30 —	45 Q (b) (4)	60 —	B.S. *f*2 (vs. control)
BioB# 4917947	2	4	25	54	85	97	99	—
B# 23MC-93 (b) (4)	1	3	15	53	83	95	99	65.97
B# 23MC-94 (b) (4)	2	5	29	43	63	84 (Fails @ S1&S2)	91	46.83 (90% CI <50)
B# 23MC-95 (b) (4)	1	3	12	39	75	94	98	52.12 (90% CI <50)
B# 5641729A (b) (4)	—	—	11	47	86	97	98	51.79 (90% CI <50)

a. Effect of variations in the (b) (4): (b) (4) The dissolution profile of the variant batch with a decrease in the concentration of (b) (4) (B# 23MC-94) yielded an *f*2 <50 (with 90% CI value <50; Table 6C) compared to the biobatch (BioB#4917947) indicating that the proposed method exhibited discriminating ability towards this CFV.

b. Effect of variations in the (b) (4): (b) (4) The dissolution profile of the variant batch with an increase in the concentration of (b) (4) (B# 23MC-95) yielded an *f*2 >50 (with 90% CI value <50; Table 6C) indicating that the proposed method exhibited limited discriminating ability towards this CFV.

c. Effect of variations in the (b) (4): The proposed product is a soft gelatin capsule, (b) (4) The dissolution profile of the variant batch with an increase in (b) (4) (B# 5641729A) yielded an *f*2 >50 (with 90% CI value <50; Table 6C) indicating that the proposed method exhibited limited discriminating ability towards this CPP/CMA.

d. Effect of variations in the (b) (4): (b) (4) are considered as CPPs. The dissolution profile of the variant batch with an increase in (b) (4) (B# 23MC-93) yielded an *f*2 >50 (Table 6C) indicating that the proposed method did not exhibit discriminating ability towards this CPP/CMA.

Thus, based on the submitted information, this Reviewer concludes that the proposed dissolution method possesses limited discriminating ability with respect to changes in the CFVs/CPPs/CMAs (towards a change in the concentration of (b) (4)).

This Reviewer notes that the inter-vessel variability (%RSD) in dissolution is high (>20%) at the first sampling time-point of 15 minutes and is in the range of 10%–20% at the second sampling time-point of 20 minutes. The high variability at the early time-points can be attributed to the time taken for the soft-gelatin capsule to rupture. Based on the mean T_{max} of the drug product ranging from 7.0 hours (fasted) to 5.0 hours (fed), the high variability in the dissolution at the early sampling time-points up to 20 minutes is not expected to have any adverse impact on the quality of the drug product.

This Reviewer notes that the Applicant proposed a two-tiered dissolution method to (b) (4) However, the proposed tier 2 method when evaluated (b) (4) exhibits a high inter-vessel variability (>20% RSD) in dissolution at all the sampling time-points. In the IR#1 response (sequence 0009; Appendix 2), the Applicant stated that the condition (b) (4) The Applicant's justification is found acceptable.

As described in the section on the "Dissolution data and acceptance criterion", based on the ability of the acceptance criterion to reject the variant batch with a decreased concentration of (b) (4), the proposed IVR method (Tier 1 and Tier 2) is found acceptable. This is with the assumption that all applicable GMPs are established and maintained for the dispensing unit operation.

B.2.2. <u>Dissolution Data and Acceptance Criterion</u>:
Based on the dissolution method (Table 5), the Applicant submitted the dissolution data of the clinical and registration batches (see Appendix 1:Table 14). Based on the dissolution data, in sequence 0001, for the three (25 mg, 50 mg and 100 mg) strengths, the Applicant proposed an acceptance criterion of:

NLT (b) (4)% (Q) is dissolved in 45 minutes

***<u>Reviewer's assessment</u>*:**
Based on the submitted dissolution data of the nine exhibit/clinical batches (three batches of each strength) at release (Appendix 1:Table 14), >85% (mean) of the drug product of the three strengths is dissolved at the 30-minute time-point. As shown below in Figures 1A–1C, the nine exhibit/clinical batches (three batches of each strength) could satisfy a specification of (b) (4)%(Q) at the (b) (4) minute time-point. Based on the simulation data using the Biopharmaceutics Automation Tool, the nine exhibit/clinical batches would satisfy a specification of (b) (4)%(Q) at the (b) (4) minute time-point at the S1/S2 stage of testing.

Figure 1A: Dissolution profiles of three batches of the 25 mg strength at release depicting the possibility (dashed-line) to satisfy an acceptance criterion of "Q= (b) (4) % in (b) (4) minutes"

Figure 1B: Dissolution profiles of three batches of the 50 mg strength release depicting the possibility (dashed-line) to satisfy an acceptance criterion of "Q= (b) (4) % in (b) (4) minutes"

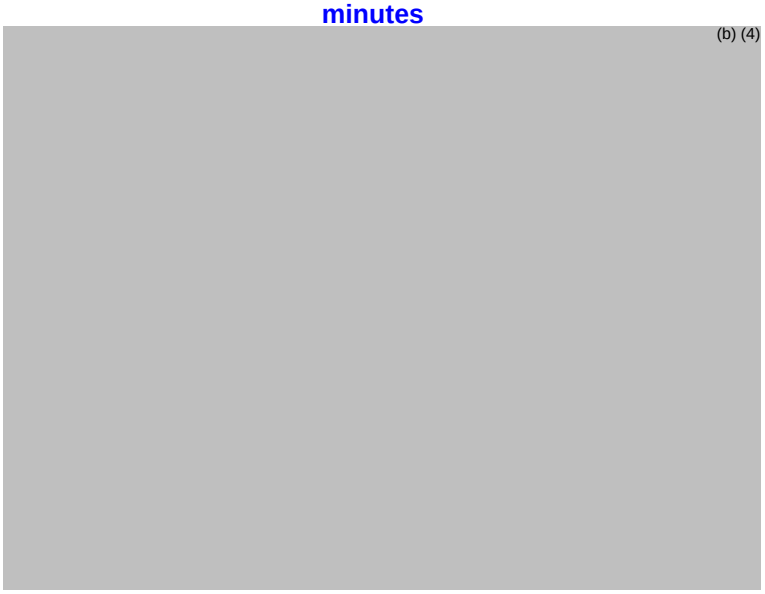
Figure 1C: Dissolution profiles of three batches of the 100 mg strength at release depicting the possibility (dashed-line) to satisfy an acceptance criterion of "Q= (b) (4)% in (b) (4) minutes"

However, as shown below in Figures 1D–1F, although the exhibit batches of the 25 mg and 50 mg strengths (Figures 1D and 1E) could satisfy a specification of (b) (4)%(Q) at the (b) (4) minute time-point through the stability period, the clinical/exhibit batches of the 100 mg strength would not satisfy a specification of (b) (4)%(Q) at the (b) (4) minute time-point through the stability period (Figure 1F).

Figure 1D: Dissolution profiles of exhibit batches of the 25 mg strength through stability depicting the possibility (dashed line) to satisfy an acceptance criterion of "Q= (b) (4)% in (b) (4) minutes"

Figure 1E: Dissolution profiles of exhibit batches of the 50 mg strength through stability depicting the possibility (dashed line) to satisfy an acceptance criterion of "Q= (b) (4)% in (b) (4) minutes

Figure 1F: Dissolution profiles of exhibit batches of the 100 mg strength through stability depicting the possibility (dashed line) to satisfy an acceptance criterion of "Q= (b) (4)% in (b) (4) minutes



Thus, based on the totality of the submitted information including the inability of variant batch# 23MC-94 to satisfy the specification of "Q= (b) (4)% in 45 minutes" at the S1 and S2 stages, the Applicant's proposed acceptance criterion is found acceptable. The final dissolution method and acceptance criterion as agreed upon by the Applicant and the FDA as shown below in Table 7.

Table 7: In vitro dissolution method and acceptance criterion proposed by the Applicant and agreed by the FDA

In vitro dissolution method Proposed (seq 0001) and agreed by the FDA				In vitro dissolution acceptance criterion Proposed (seq 0001) and agreed by the FDA
Source	**Apparatus**	**Medium/ Volume**	**Agitation speed/ Temperature**	
In-house	USP apparatus 1 (20 mesh)	Tier 1: 900 mL of 0.6% SDS in 0.1 N HCl Tier 2: "A" – first 12 min: 800 mL of 0.1 N HCl + Pepsin, 750,000 U/L "B" – after 12 min: 100 mL of 5.5% SDS in 0.1 N HCl	Speed: 100 rpm Temp: 37 °C	NLT (b) (4)% (Q) in 45 minutes

B.2.3. IVR data during stability:

Stability studies were conducted on three exhibit/clinical batches of the three strengths as shown below in Tables 8A–8C using the proposed dissolution method/acceptance criterion. Primary stability data was generated under long term (25 °C/60% RH), accelerated (30 °C/65% RH) and more severe stressed (40 °C /75% RH) storage conditions.

Table 8A: Details of batches of the 25 mg strength placed on stability

Bulk Lot	Manufacturer	Date of Manufacture	Drug Substance Batch	Lot Size (Capsules)	Packaged Lot	Date of Packaging	Packaging Description	Stability Type	Available Stability Data (Months)
4940538	(b) (4)	01 Apr 2022	38003495	(b) (4)	1954763	7 Dec 2022	(b) (4)	Primary (Registration)	9
4940539		02 Apr 2022	38003496		1954764	9 Dec 2022		Primary (Registration)	9
4940540		04 Apr 2022	38003508		1954765	9 Dec 2022		Primary (Registration)	9
4940538		01 Apr 2022	38003495		1905131	17 May 2022		Supportive	15
4940539		02 Apr 2022	38003496		1905132	18 May 2022		Supportive	15
4940540		04 Apr 2022	38003508		1905133	20 May 2022		Supportive	15

Table 8B: Details of batches of the 50 mg strength placed on stability

Bulk Lot	Manufacturer	Date of Manufacture	Drug Substance Batch	Lot Size (Capsules)	Packaged Lot	Date of Packaging	Packaging Description	Stability Type	Available Stability Data (Months)
4924010	(b) (4)	21 Mar 2022	38003495	(b) (4)	1954766	12 Dec 2022	(b) (4)	Primary (Registration)	9
4924011		22 Mar2022	38003496		1954766	12 Dec 2022		Primary (Registration)	9
4924012		23 Mar 2022	38003508		1954768	13 Dec 2022		Primary (Registration)	9
4924010		21 Mar 2022	38003495		1905134	16 May 2022		Supportive	15
4924011		22 Mar2022	38003496		1905135	16 May 2022		Supportive	15
4924012		23 Mar 2022	38003508		1905136	17 May 2022		Supportive	15

Table 8C: Details of batches of the 100 mg strength placed on stability

Bulk Lot	Manufacturer	Date of Manufacture	Drug Substance Batch	Drug Substance Source	Lot Size (Capsules)	Packaged Lot	Date of Packaging	Packaging Description	Stability Type	Available Stability Data (Months)
4917947	(b) (4)	08 Mar 2022	38003495	(b) (4)	(b) (4)	1905137	10 May 2022	(b) (4)	Primary (Registration)	15
4917949		09 Mar 2022	38003496			1905138	11 May 2022		Primary (Registration)	15
4924028		07 Mar 2022	38003508			1905139	12 May 2022		Primary (Registration)	15

***Reviewer's assessment*:**
The dissolution method and acceptance criterion as shown above in Table 7 have been proposed for the QC of the drug product at release and through the stability period. Assessment of the stability data is under the purview of the CMC/DP Reviewer.

B.3. CLINICAL RELEVANCE OF IVR METHOD AND ACCEPTANCE CRITERION (e.g., *IVIVR/IVIVC, In silico modeling, small scale in vivo*):
Assessment: Adequate

***Reviewer's assessment*:**
The Applicant has not performed an IVIVR/IVIVC nor any modeling studies. Although the proposed drug product is an immediate release product, the T_{max} ranges from 7.0 hours (fasted) to 5.0 hours (fed). The long T_{max} for the immediate release drug product may be attributed to the crinecerfont API being a low-solubility/low-permeability (BCS class 4) drug substance. Based on the submitted data, the proposed dissolution method and acceptance criterion do not possess any clinical relevance and primarily serve to ensure batch-to-batch consistency, and this is acceptable.

B.12. BRIDGING OF PRODUCTS:
Assessment: Adequate

***Bridging of Formulations*:**
***Reviewer's assessment*:**
The soft-gelatin capsule is the final to-be-marketed (TBM) commercial formulation. The TBM drug product is proposed in three (25 mg, 50 mg and 100 mg) strengths. The composition of the three strengths of the TBM formulation is shown below in Table 9A. The capsule fill formulation of the three strengths is compositionally proportional to each other.

Table 9A: Composition of the TBM formulation

Strength		25 mg		50 mg		100 mg	
Ingredient	**Function**	**Weight per unit dose (mg)**	**% per unit dose (w/w)**	**Weight per unit dose (mg)**	**% per unit dose (w/w)**	**Weight per unit dose (mg)**	**% per unit dose (w/w)**
Crinecerfont	Active Ingredient	25.0	(b) (4)	50.0	(b) (4)	100.0	(b) (4)
Medium-Chain Triglycerides	(b) (4)			(b) (4)		(b) (4)	
Propylene Glycol Dicaprylate/Dicaprate							
Lauroyl Polyoxyl-32 Glycerides							
Vitamin E Polyethylene Glycol Succinate							
Total			100.0		100.0		100.0
Type of Gelatin Used per Capsule							
Gelatin	Function	25 mg		50 mg		100 mg	
Gold gelatin	Capsule Shell	NA	NA	one side	one side	both sides	both sides
Orange gelatin	Capsule Shell	both sides	both sides	one side	one side	NA	NA

Phase 3 studies were conducted on the 50 mg hard-gelatin capsule. The qualitative and quantitative composition of the capsule fill formulation is identical for the Phase 3 capsule formulation and the TBM formulation (Table 9B).

Table 9B: Composition of the Phase 3 50 mg hard-gelatin capsule

Ingredient	**Function**	**% per unit dose (w/w)**	**Weight per capsule (mg)**
Crinecerfont	Active Ingredient	(b) (4)	50.0
Medium-Chain Triglycerides (b) (4)	(b) (4)		
Propylene Glycol Dicaprylate/Dicaprate (b) (4)			
Lauroyl Polyoxyl-32 Glycerides (b) (4)			
Vitamin E Polyethylene Glycol Succinate			
Hard Gelatin Capsule Shell, (b) (4) (b) (4)			
Gelatin Powder, (b) (4) (b) (4)			
Total Fill Solution Weight		100.0	(b) (4)

A Phase 1 comparative bioavailability study (S# NBI-74788-1736) was conducted to bridge the 100 mg strength of the TBM product to the Phase 3 50 mg hard-gelatin capsule. The 90% CI values of the geometric means of the PK parameters (C_{max}, $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-inf}}$) complied with the acceptance criterion range of 0.8–1.25 (Table 10). Assessment of S# NBI-74788-1736 is under the purview of the OCP/Clinical Pharmacology assessor. Although a comparison of the dissolution data of 2 × 50 mg Phase 3 capsules and 1 × 100 mg TBM capsules yielded an $f2$ <50 (Table 10), this Reviewer concludes that since the comparative dissolution studies were conducted in the proposed dissolution method (Table 7), the proposed dissolution method that was optimized for the TBM soft-gelatin capsule may not have been optimal for the Phase 3 hard-gelatin capsule.

Table 10: Statistical comparison of PK parameters (90% CI values) and *in vitro* dissolution profiles (*f*2) of 100 mg (2 × 50 mg) Phase 3 capsules and 100 mg (1 × 100 mg) TBM capsules

Phase 1 S# NBI-74788-1736		*In vitro* dissolution
PK Parameters	90% CI values of geometric mean ratios of 100 mg (2 × 50 mg) Phase 3 capsules and 100 mg (1 × 100 mg) TBM capsules	*f*2 comparison of 100 mg (2 × 50 mg) Phase 3 capsules and 100 mg (1 × 100 mg) TBM capsules
C_{max} (ng/mL)	0.98–1.16	33.33
$AUC_{0\text{-tlast}}$ (ng.h/mL)	0.94–1.09	
$AUC_{0\text{-inf}}$ (ng.h/mL)	0.91–1.18	

Based on the 90% CI values of the PK parameters (C_{max}, $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-inf}}$) complying with the acceptance criterion range of 0.8–1.25, the 100 mg strength of the TBM product (soft-gelatin capsule) can be considered to be satisfactorily bridged to the 50 mg strength of the Phase 3 clinical hard-gelatin capsule.

***Bridging of additional/lower (25 mg and 50 mg) strengths*:**
A Phase 1 PK study (S# NBI-74788-1736) was conducted on the TBM formulation of the 100 mg strength. In accordance with 21 CFR 320.22(d), the Applicant proposed to establish a bridge between the TBM formulation of the 25 mg and 50 mg strengths and the TBM formulation of the 100 mg strength based on –

- Crinecerfont exposure (C_{max} and AUC) parameters following single oral doses of crinecerfont are dose-proportional over a clinically relevant dose range for the capsule formulation (25 to 200 mg).
- The manufacturing process for the fill formulation, and the qualitative and quantitative composition are proportional across the 100 mg, 50 mg and 25 mg strengths of the TBM capsule.
- The 25 mg and 50 mg registration capsules have similar in-vitro dissolution profiles, as compared to the 100 mg TBM capsule and 2 × 50 mg Phase 3 capsules, respectively.
- The reference product (100 mg TBM capsule) used for *in vitro* comparison was demonstrated to be bioequivalent to the Phase 3 capsule in an *in vivo* clinical study.

***Reviewer's assessment*:**
A Phase 1 study was conducted on the TBM formulation of the 100 mg strength. In accordance with 21 CFR 320.22(d)(2), in support of the bridge between the TBM formulation of the 25 mg and 50 mg strengths and the TBM formulation of the 100 mg strength, the Applicant submitted data demonstrating that –

- Crinecerfont exposure (C_{max} and AUC) parameters following single oral doses of crinecerfont are dose-proportional over a clinically relevant dose range for the capsule formulation (25 to 200 mg).

- The manufacturing process for the fill formulation, and the qualitative and quantitative composition are proportional across the 100 mg, 50 mg and 25 mg strengths of the TBM capsule (Table 9A).

- The reference product (100 mg TBM capsule) used for *in vitro* comparison was demonstrated to be bioequivalent to the Phase 3 capsule in an *in vivo* clinical study (S# NBI-74788-1736; Table 10).

- A comparison of the in vitro dissolution profile data (*f*2 values) between the TBM 100 mg capsule (1 × 100 mg) and the TBM 25 mg (as 4 × 25 mg and 1 × 25 mg [% label claim]) and 50 mg (as 2 × 50 mg and 1 × 50 mg [% label claim]) registration capsules is shown below in Table 11.

Table 11: Comparative dissolution data (*f*2 values) between the TBM 100 mg capsule (1 × 100 mg; BioB# 4917947) and the TBM 25 mg (as 4 × 25 mg; B# 4824382 and 1 × 25 mg; B# 4940538 [% label claim]) and 50 mg (as 2 × 50 mg and 1 × 50 mg [% label claim]) registration capsules

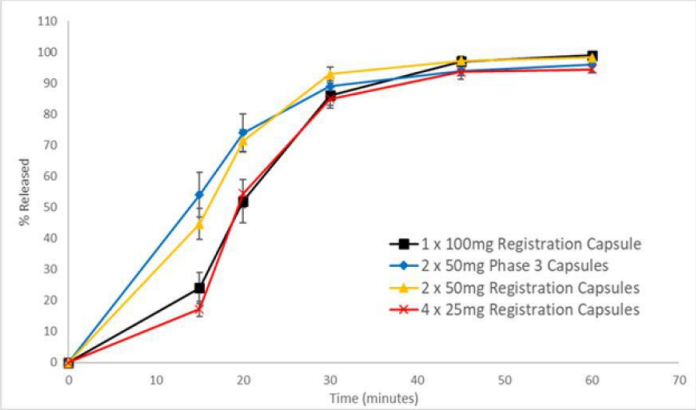
Strength and Batch information	50 mg		25 mg	
	100 mg (2 × 50 mg) B# 4824386	50 mg (% LC) (1 × 50 mg) B# 4924010	100 mg (4 × 25 mg) B# 4824382	25 mg (% LC) (1 × 25 mg) B# 4940538
100 mg (1 × 100 mg) BioB# 4917947	33.6	24.35	68	40.34

Based on the submitted information, the 100 mg (1 × 100 mg) TBM capsule exhibits a dissolution profile that is similar (*f*2 >50) to 100 mg (4 × 25 mg) TBM capsules. However, the dissolution profile of 100 mg (2 × 50 mg) TBM capsules differs (*f*2 <50) from the 100 mg (1 × 100 mg) TBM capsule.

This Reviewer notes that the dissolution profile of the 100 mg (1 × 100 mg) TBM capsule differs (*f*2 <50) from the 25 mg as % LC (1 × 25 mg) and the 50 mg as % LC (1 × 50 mg) TBM capsules.

In support the waiver of *in vivo* bioavailability studies for the 25 mg and 50 mg strengths of the TBM capsules, in response to IR#1 (sequence 0009; Appendix 2), the Applicant stated that although the dissolution profile of the 2 × 50 mg registration capsule (Figure 2) was faster than the 1 × 100 mg and 4 × 25 mg registration capsules, the dissolution profile of the 2 × 50 mg registration capsule was similar (*f*2 = 61) to the 2 × 50 mg Phase 3 capsule – that was demonstrated to be bioequivalent to the 1 × 100 mg registration capsule (Table 10).

Figure 2: Mean (±SD) dissolution profiles of 2 × 50 mg Crinecerfont Phase 3 Capsules and 4 × 25 mg, 2 × 50 mg, and 1 × 100 mg Crinecerfont Registration Capsules



The faster dissolution profile observed for the 2 × 50 mg Phase 3 and TBM capsules versus the 1 × 100 mg and 4 × 25 mg TBM capsules (Tables 12A and 12B) could be attributed to the shorter disintegration times for the 50 mg capsules (Table 12C).

Table 12A: Comparative dissolution data (*f*2 values) between the 2 × 50 mg Phase 3 capsule versus the 2 × 50 mg TBM, 1 × 100 mg TBM and 4 × 25 mg TBM capsules

Strength and Batch information	100 mg (2 × 50 mg TBM) B# 4824386	100 mg (1 × 100 mg TBM) BioB# 4917947	100 mg (4 × 25 mg TBM) B# 4824382
100 mg (2 × 50 mg Phase 3) B# 0000889795	61	33.3	30.6

Table 12B: Comparative dissolution data (*f*2 values) between the 2 × 50 mg TBM capsule versus the 2 × 50 mg Phase 3, 1 × 100 mg TBM and 4 × 25 mg TBM capsules

Strength and Batch information	100 mg (2 × 50 mg Phase 3) B# 0000889795	100 mg (1 × 100 mg TBM) BioB# 4917947	100 mg (4 × 25 mg TBM) B# 4824382
100 mg (2 × 50 mg TBM) B# 4824386	61	33.6	35.1

Table 12C: Capsule disintegration time in 0.1 N HCl with 0.6% SDS at 37 °C (n = 6)

Drug Product	Average Disintegration Time (MM:SS)	Range (MM:SS)
Registration Capsules, 25 mg	(b) (4)	(b) (4)
Registration Capsules, 50 mg		
Registration Capsules, 100 mg		
Phase 3 Capsules		

Based on the data that the 2 × 50 mg Phase 3 capsules is bioequivalent to the 1 × 100 mg registration capsule (Table 10) and the three strengths of the TBM capsules satisfying the acceptance criterion of "Q = (b) (4)% in 45 minutes", this Reviewer concludes that the observed differences in dissolution profile between the 2 × 50 mg TBM capsule and the 1 × 100 mg and the 4 × 25 mg TBM capsules would not be expected to have an adverse

impact on *in vivo* PK parameters of the drug product following administration of 2 × 50 mg registration capsules.

Thus, based on the totality of the submitted data, this Reviewer concludes that a bridge between the 25 mg/50 mg TBM formulations and the 100 mg TBM formulation has been satisfactorily established, and an additional *in vivo* BE study for the lower (25 mg and 50 mg) strengths is not required.

***Bridging of Manufacturing sites and Batch sizes*:**

***Reviewer's assessment*:**
A single site (b) (4) has been used to manufacture the TBM batches of the three strengths (Appendix 1:Table 14). Phase 1 studies were conducted on the 100 mg strength of the TBM product. Thus, a bridging of manufacturing sites is not required.

The batch size of the TBM exhibit/clinical batches of the three strengths manufactured at (b) (4) (Appendix 1:Table 14) is (b) (4) capsules. Since the range of the sizes of the exhibit/clinical batches are within 10× of each other, bridging of the exhibit/clinical batches based on the Phase 1 studies is found acceptable. The size of the intended commercial batches of the three strengths is (b) (4) capsules. Since the range of the sizes of the exhibit/clinical and intended commercial batches are within a factor of 10 times of each other (Table 13), based on the SUPAC-IR *Guidance*, an in vitro dissolution profile comparison between exhibit/clinical and intended commercial batches is recommended to bridge the intended commercial batches to the clinical batch.

Table 13: Details of manufacturing site and sizes of the clinical/exhibit and commercial batches

Manufacturer	Batch size		
	25 mg	50 mg	100 mg
(b) (4)	(b) (4) caps (exhibit and commercial)	(b) (4) caps (exhibit and commercial)	(b) (4) caps (Phase 1, exhibit and commercial)

B.13. BIOWAIVER REQUEST:

Assessment: Adequate

***Reviewer's assessment*:**
Based on the totality of the information submitted in support of the bridging across the formulations, additional strengths, manufacturing sites and batch sizes, this Reviewer finds the data in support of a waiver for demonstration of *in vivo* bioequivalence for the 25 mg and 50 mg strengths of the TBM formulation in accordance with 21 CFR 320.22(d)(2) to be acceptable. An additional *in vivo* study is not required. The efficacy studies for the 25 mg and 50 mg strengths will be assessed by the Clinical/Clinical Pharmacology Reviewer.

R. REGIONAL INFORMATION:

Life Cycle Management Considerations and Risk Mitigation Strategies

***Reviewer's assessment*:**
The proposed drug product is an immediate-release product wherein the T_{max} ranges from 7.0 hours (fasted) to 5.0 hours (fed). The long T_{max} for the immediate-release drug product may be attributed to the crinecerfont API being a low-solubility/low-permeability (BCS class 4) drug substance.

The proposed dissolution method possesses limited discriminating ability with respect to a change in the concentration of (b) (4) The Applicant's approach of establishing the concentration of (b) (4) and the proposed/agreed upon acceptance criterion maintain the risk from a Biopharmaceutics perspective at a low level. This is with the assumption that all applicable GMPs are established and maintained for the dispensing unit operation.

BIOPHARMACEUTICS PENDING DEFICIENCIES:
None

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Haritha Mandula

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Date: 9/06/2024 01:14:07PM
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Rajesh Savkur

Digitally signed by Rajesh Savkur
Date: 9/06/2024 01:13:04PM
GUID: 5a4fe3d5001e3750f54a8daadb2faa06

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

/s/

AKM KHAIRUZZAMAN
10/07/2024 01:02:04 PM
This NDA is recommended for approval from Product Quality Perspective.

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 218820
Assessment # 1

Drug Product Name	CRENESSITY (Crinecerfont)
Dosage Form	Oral solution
Strength	50 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Neurocrine Biosciences Inc.
US agent, if applicable	N/A
Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	N/A
Maximum Daily Dose	200 mg/day
Alternative Methods of Administration	None

Submission(s) Assessed (eCTD Sequence)	Document Date	Discipline(s) Affected
0001	04/30/2024	Quality (Original NDA submission)
0002	05/17/2024	Quality
0003	06/14/2024	Quality
0004	06/18/2024	Quality
0005	07/02/2024	Quality
0006	07/08/2024	Quality
0007	08/07/2024	Quality
0008	08/13/2024	Quality
0009	08/23/2024	Quality
0010	10/02/2024	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Stephanie Springer	Zhengfu Wang
Drug Product	Jennifer McCord	Akm Khairuzzaman
Manufacturing	Laurie Nelson	Sateesh Sathigari
Microbiology	Jianli Xue	Nandini Bhattacharya
Biopharmaceutics	Rajesh Savkur	Haritha Mandula
Environmental	Jennifer McCord	Akm Khairuzzaman
Regulatory Business Process Manager	Oluwafunmike Ajomale	
Application Technical Lead	Akm Khairuzzaman	

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. **DMFs:** Acceptable.

DMF No.	Type	Holder	Item Referenced	Status	Comments
(b) (4)	IV	(b) (4)		Active	Appropriate LoA provided
	III			Active	Appropriate LoA provided
	III			Active	Appropriate LoA provided
	III			Active	Appropriate LoA provided

B. OTHER DOCUMENTS: ***IND, RLD, RS, Approved NDA***

None

2. CONSULTS The Office of Pharmaceutical Quality Research (OPQR), OPQ was consulted for analytical method verification.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 218820 is recommended for approval. As part of this action, an expiration period of 18 months for the product, stored under refrigerated condition at 2°C - 8°C (36° F to 46° F) in the commercial packaging, is granted. Once a bottle is opened for use, it may be stored under refrigeration at 2°C to 8°C (36°F to 46°F) or at room temperature (15°C to 25°C [59°F to 77°F]) for up to 30 days.

II. SUMMARY OF QUALITY ASSESSMENTS

In accordance with section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, the applicant Neurocrine Biosciences Inc. submitted NDA 218820 to seek marketing approval for CRENESSITY™ (crinecerfont) oral solution, for oral use. Crinecerfont is a new chemical entity (NME). Its identity, purity, impurity, and manufacturing are adequately controlled through appropriate quality management system and validated analytical methods. The drug substance is stable for the intended storage period in its commercial packaging system. The new drug product is an oral solution whereby the poorly soluble drug substance (b) (4) Other excipients used in the formulation are acceptable. The drug product is supplied in one strength (50 mg/mL) which is packaged in a compatible 60 mL polyethylene terephthalate (PET) bottle with child-resistant cap. The drug product manufacturing process is adequately controlled by the quality management system of the listed cGMP compliant manufacturing facilities. From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, potency, and stability.

A. Quality Assessment Overview

Drug Substance: Adequate

Crinecerfont, a new synthetic small molecule that has one stereocenter in the S configuration. Sufficient characterization is provided to assure the identity and purity of the drug substance. The drug substance structure has been characterized adequately using ^{1}H NMR, ^{13}C NMR, elemental analysis, FTIR, MS, and single crystal X-ray structure determination. Absolute configuration of the stereocenter is confirmed by X-ray crystal structure. The commercial manufacturing process yields the drug substance as a single polymorph (b) (4) The drug substance is BCS Class 4. However, particle size and polymorphism of the drug substance are not critical quality attributes because the drug product is a solution. The applicant has used the well-established synthesis for

manufacture of the drug substance which adequately controls residual solvents, elemental impurities, and mutagenic impurities as per the applicable ICH guidance. Starting materials are appropriately designated. The drug substance quality control specification includes relevant quality attributes such as description, identification by FTIR and HPLC, assay, chiral purity, water content, organic impurities, and microbial limits. Analytical methods to control the quality of the drug substance are adequate and appropriately validated. Stability data support the proposed re-testing period of (b) (4) months when stored (b) (4) For additional information, please refer to Dr. Stephanie Springer's review in Panorama dated 08/8/2024.

Drug Product: Adequate

Crinecerfont drug product is an oral solution that is available in one strength (50 mg/mL), packaged in a compatible 60 mL polyethylene terephthalate (PET) bottle with child-resistant cap. The drug product is formulated as solution using excipients such as medium chain triglycerides (MCT), (b) (4), Butylated Hydroxytoluene, saccharin, and orange flavor (b) (4) Other than the orange flavor, all excipients are compendial, controlled by USP/NF standards and are used in amounts within the limits of the FDA's IIG database. There are no novel excipients and no excipients of human or animal origin. No (b) (4) were proposed. There is no change in the formulation composition between the commercial product and the Phase 3 trial product. (b) (4) as a result, particle size of the drug substance was determined to not impact the product quality. During the product development, critical quality attributes were identified, and they are adequately controlled by product specification which includes tests for description, identification, assay, degradation products, (b) (4) assay, deliverable volume, clarity, viscosity, and microbial attributes. All analytical methods for quality control of the product are adequate and they are appropriately validated. Based on the provided stability data, the Applicant's proposed shelf-life of 18 months is acceptable when stored under long-term refrigerated conditions (2 °C – 8 °C). For additional information, please refer to Dr. Jennifer McCord's review in Panorama dated 10/04/2024.

Labeling: Adequate

Updated labeling information is found to be adequate by the chemistry reviewer, Dr. Jennifer McCord. Minor edits were made in the chemistry section of the package insert.

Manufacturing: Adequate

The drug product is manufactured (b) (4) The manufacturing process

reviewer, Dr. Laurie Nelson concludes that the manufacturing process is adequately controlled by appropriate control strategy, including in-process controls.

Biopharmaceutics: Adequate

The drug product is an oral solution. (b) (4) Based on the drug product being a true solution, Dr. Rajesh Savkur concludes that an in vitro quality control dissolution testing is not required and the risk from a Biopharmaceutics perspective is low.

Microbiology (if applicable): Adequate

Overall, the microbiological attributes of the drug product are found to be adequate by the Microbiology reviewer, Dr. Jianli Xue

Manufacturing Facilities: Adequate

Based on the inspection (PAI), inspection history, manufacturing experience and acceptable compliant status, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended an overall approval for all the currently listed manufacturing and testing facilities concerning this NDA.

B. Risk Assessment: Overall quality risk is low

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Assay (API), stability	Medium to Low	(b) (4)	Low	(b) (4)
Assay (b) (4) **)**	Low		Low	
Physical stability (phase separation)	Medium to low		Low	

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Physical stability (solid state)	Low	(b) (4)	Low	(b) (4)
Degradation impurities	Medium to low		Low	
Leachable extractables	Low		Low	
Palatability	Low		Low	
Leachable Extracts	Low		Low	
Dosing accuracy	Low		Low	
Microbial limits	Low		Low	

C. List of Deficiencies for Complete Response:

None

Application Technical Lead Name and Date:

Akm Khairuzzaman, Ph.D.10/07/2024

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	NDA 218820
Assessment Cycle Number	1
Drug Product Name	CRENESSITY

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**0001**
Patient Information	Adequate	**0001**
Instruction for Use (IFU)	Adequate	**0001**
Container Labels	Adequate	**0001**
Carton Labeling	Adequate	**0001**

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
SDN # 0001	04/30/2024	All labeling

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	Crinecerfont oral solution
Route(s) of administration	Adequate	Adequate after removing (b) (4)
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval [§201.57(a)(3)]	Adequate	202X
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	50 mg/mL
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	Not a salt

[2] Draft guidance: *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)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *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); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	N/A
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	N/A

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *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 <659>
[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

Pediatric patients weighing 10 kg to <20 kg	25 mg twice daily (50 mg per day)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	N/A
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	N/A
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	N/A
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	N/A

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	N/A

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Capsules and Oral solution
Strength(s) in metric system	Adequate	50 mg/mL
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	Not a salt
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	Light yellow to orange oral solution
Assess if the tablet is scored. If product meets guidelines and	N/A	N/A

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
criteria for a scored tablet, state "functionally scored."		
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	N/A

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[redacted]

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	Present
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	Not a salt
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	Adequate following edits (as marked above)
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and	N/A	N/A

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statement of effect. [§ 201.100(b)(5)(iii)].		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	N/A
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	N/A
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	corticotropin-releasing factor type 1 receptor antagonist
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	2-thiazolamine, 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-2-propyn-1-yl; structure and molecular weight present
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	N/A	N/A
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	Not present
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Adequate	Adequate following edit (b) (4)
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is	N/A	No monograph for the drug product

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).		

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Oral Solution
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the	Adequate	50 mg/mL

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
active moiety. No equivalency statement.		
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Adequate following edit (b) (4)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	light yellow to orange, orange-flavored liquid
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	N/A
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	Store unopened bottles under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	2°C to 8°C (36°F to 46°F)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	N/A	N/A
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	Adequate following addition

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Clinical has added a comment to the Applicant to add this information; once added, this will be adequate.

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	Crinecerfont
Special preparation instructions (if applicable).	N/A	N/A
Storage and handling information (if applicable).	Adequate	Store unopened CRENESSITY oral solution refrigerated at 2° to 8°C (36° to 46°F). Do not freeze.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	N/A
Active ingredient(s) (if applicable).	Adequate	Crinecerfont
Alphabetical listing of inactive ingredients (if applicable).	N/A	N/A; product for oral use

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Distributed by: Neurocrine Biosciences, Inc., San Diego, CA 92130, U.S.A

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(b) (4)

[redacted]

[25] Carton and Container Labeling Resources

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

3.2 Carton Labeling

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	Crenessity (Crinecerfont)

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	50 mg/mL
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	For Oral administration only
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	N/A
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	30 mL
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	Present
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	Present
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	Present
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	Store in refrigerator at 2 °C to 8 °C
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms	N/A	Yes	N/A

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Yes	N/A; oral drug
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	N/A
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	Present
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	(b) (4)
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	Distributed by: Neurocrine Biosciences, Inc.
"Keep out of reach of children" statement, optional for Rx,	Adequate	Yes	Present

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
required for OTC [§ 201.66(c)(5)(x)].			
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	N/A; no medication guide
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	N/A; no USP monograph
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]	N/A	Yes	N/A
And others if space is available.	N/A	Yes	N/A

Assessment of Carton Labels and Container Labeling: *Adequate*

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

[31] USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these issues in this section.

Primary Labeling Assessor Name and Date: Jennifer McCord, 09/06/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Jennifer McCord

Digitally signed by Jennifer McCord
Date: 9/09/2024 02:27:11PM
GUID: 63221b9c007a3580cbffb5160db88fe7

Akm Khairuzzaman

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-218820-ORIG-1
Submission History	4/30/2024 (Sequence 0001): Original submission
Drug Product Name/ Strength	CRENESSITY™ – Crinecerfont oral solution, 50 mg/mL
Route of Administration	Oral
Applicant Name	Neurocrine Biosciences Inc.
Therapeutic Classification/ OND Division	Division of General Endocrinology (DGE)
Proposed Indication	(b) (4)
IND Number	IND-132849
Primary Reviewer	Rajesh Savkur, Ph.D.
SPQA	Haritha Mandula, Ph.D.
Assessment Recommendation	**Adequate**

EXECUTIVE SUMMARY

In this submission, the Applicant seeks approval of CRENESSITY™ – Crinecerfont oral solution, 50 mg/mL. Crinecerfont, a selective corticotropin releasing factor 1 (CRF1) receptor antagonist, has been developed (b) (4) NDA-218820-ORIG-1 was initially submitted to the Division of General Endocrinology (DGE) on 4/30/2024 under section 505(b)(1). The proposed drug product (CRENESSITY – Crinecerfont oral solution, 50 mg/mL) comprises of a poorly aqueous soluble active pharmaceutical ingredient (API), crinecerfont, (b) (4) The recommended dosage of the drug product for patients 4 years of age and older is shown below, and should be taken with food, twice daily (in the morning and evening).

Age and Body Weight	Dosage Regimen
Adults (18 and older) Pediatric patients weighing ≥55 kg	100 mg twice daily (200 mg per day)
Pediatric patients weighing 20 kg to <55 kg	50 mg twice daily (100 mg per day)
Pediatric patients weighing 10 kg to <20 kg	25 mg twice daily (50 mg per day)

***Assessment Summary*:**
The Biopharmaceutics assessment focuses on evaluating (i) the Applicant's proposal to exclude the in vitro dissolution test from the finished drug product specifications, and (ii) the bridging data between the clinical and commercial/to-be-marketed drug products, the manufacturing sites and batch sizes.

- ***In vitro* dissolution method and acceptance criterion:**
  The proposed drug product contains a low-solubility drug substance and is formulated as a solution using Medium-Chain Triglycerides and Propylene Glycol (b) (4), and Lauroyl Polyoxyl-32 Glyceride and Vitamin E Polyethylene Glycol Succinate (b) (4). Based on the CMC/DP Reviewer's assessment, the (b) (4) therefore the drug product is a true solution (b) (4). Based on the drug product being a true solution, the dissolution test/acceptance criterion are not required as part of the finished drug product specifications to ensure QC of the drug product.

  The proposed drug product is an immediate-release product (b) (4) Based on the drug product being a true solution, the risk from a Biopharmaceutics perspective is low. Further risk mitigation is not required (Table 1).

Table 1: Risk Assessment

Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Low	• The drug product is an immediate-release product. • (b) (4) • The drug product is a true solution.	Low	• Further risk mitigation is not required.

- **Product Bridging:**
  Bridging of drug product formulations across product development:
  The oral solution is the final to-be-marketed (TBM) commercial formulation. The TBM drug product is proposed in a single (50 mg/mL) strength. Phase 1 and Phase 3 studies

were conducted on the final to-be-marketed (TBM) commercial formulation. Thus, bridging of formulations is not required.

Bridging of manufacturing sites:
A single site (b) (4) has been used to manufacture the TBM batches of the proposed drug product. Phase 1 and Phase 3 studies were conducted on the drug product manufactured at (b) (4) Thus, bridging of manufacturing sites is not required.

Bridging of batch sizes:
The size of the Phase 1/Phase 3 batch manufactured at (b) (4) is (b) (4) The proposed commercial batch size for the drug product manufactured at (b) (4) is (b) (4) Thus, bridging of batch sizes is not required.

- **Biowaiver request:**
  Phase 1 and Phase 3 studies were conducted on the TBM product. The Applicant has not requested a waiver of bioavailability studies. The efficacy studies will be assessed by the Clinical/Clinical Pharmacology Reviewer.

The list of submissions assessed in the NDA are shown below in Table 2.

Table 2: List of Submissions Being Assessed

IND/NDA	eCTD sequence #	Date of submission	Document
NDA	0001	4/30/2024	Original Submission

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*:
None

OVERALL BIOPHARMACEUTICS RECOMMENDATION:
From a Biopharmaceutics perspective, NDA-218820-ORIG-1 for CRENESSITY – Crinecerfont oral solution, 50 mg/mL, is **adequate** and is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

B.1. BCS DESIGNATION:

Assessment: Not Applicable

Solubility:

The active pharmaceutical ingredient (API), crinecerfont, is a white to light yellow solid that is poorly soluble in water and is highly soluble in organic solvents (Tables 3A and 3B). The solubility of the crinecerfont drug substance across the physiological pH range of 1 to 6.8 is <0.01 mg/mL (Table 3C).

Table 3A: Physicochemical properties of the crinecerfont API

Physical/Chemical Properties	Description
Appearance	White to light yellow solid
Dissociation constant[a]	pKa = 4.11 (calculated)
Partition coefficient[a]	Log P = 7.75 (calculated)
Optical activity (specific rotation)	$[\alpha]_D$: - 186.1° (determined at 20 °C with a 10 mg/mL solution in methanol)
Melting point	Melt endotherm with an onset of 87 °C
Hygroscopicity	Non-hygroscopic
Crystallinity	Crystalline
Polymorphism	(b) (4)
Morphology	Plate-like crystals
Solubility	Solubility data at 25 °C
Biopharmaceutical Classification System (BCS)	Class 4

Table 3B: Solubility data of the crinecerfont API in aqueous and organic solvents

Solvent	Solubility at 25°C (mg/mL)
Acetone	> 531
Acetonitrile	187
t-Butyl methyl ether	340
Dichloromethane	> 814
Ethanol	28
Ethyl acetate	508
n-Heptane	26
Isopropyl alcohol	15
Methanol	25
Tetrahydrofuran	782
Toluene	572
Water	< 0.01
Water (pH 1 – 9)[a]	< 0.01

[a] Solubility measured at 9 points in buffer systems from pH 1 to pH 9. All measurements were < 0.01 mg/ml.

Table 3C: Aqueous solubility data of the crinecerfont API in the pH range of 1.0 to 9.0

Aqueous Media	Solubility (mg/mL)
pH 1.0 USP Buffer	< 0.01
pH 2.0 USP Buffer	< 0.01
pH 3.0 USP Buffer	< 0.01
pH 4.0 USP Buffer	< 0.01
pH 5.0 USP Buffer	< 0.01
pH 6.0 USP Buffer	< 0.01
pH 7.0 USP Buffer	< 0.01
pH 8.0 USP Buffer	< 0.01
pH 9.0 USP Buffer	< 0.01
DI Water (pH 8.5 at saturation)	< 0.01

Permeability:
The apparent permeability (P_{app}) of the API (using [^{14}C]crinecerfont) across Caco-2-TC7 cell monolayers was 2.2×10^{-7} cm/s.

***Reviewer's assessment*:**
The concentration of the crinecerfont API in the drug product is 50 mg/mL. Based on the aqueous solubility being <0.01 mg/mL, the crinecerfont API would not be soluble in the aqueous solvents across the physiological pH range of 1 to 6.8. Thus, the crinecerfont API can be considered as a low-solubility drug substance.

The crinecerfont API exhibits a low apparent permeability (P_{app}) of 2.2×10^{-7} cm/s.

Based on the low-solubility and low-permeability, the Applicant has classified the crinecerfont API as a BCS class 4 compound. Since the Applicant has not requested a formal claim for the BCS designation, the permeability and BCS class of the crinecerfont API have not been assessed.

B.2. IN VITRO DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

Assessment: Adequate

The proposed drug product contains a low-solubility drug substance and is formulated as a solution using Medium-Chain Triglycerides and Propylene Glycol (b) (4), and Lauroyl Polyoxyl-32 Glyceride and Vitamin E Polyethylene Glycol Succinate (b) (4) Based on the drug product being a true solution, the dissolution test/acceptance criterion have not been proposed as part of the finished drug product specifications at release and through stability.

***Reviewer's assessment*:**
The proposed drug product contains a low-solubility drug substance and is formulated as a solution using Medium-Chain Triglycerides and Propylene Glycol (b) (4), and Lauroyl Polyoxyl-32 Glyceride and Vitamin E Polyethylene Glycol Succinate (b) (4) Based on the CMC/DP Reviewer's assessment, (b) (4) the drug product is a true solution (b) (4). Based on the drug product being a true solution, this

Reviewer concludes that the dissolution test/acceptance criterion are not required as part of the drug product specifications to ensure QC of the drug product. Thus, the Applicant's proposal to exclude the dissolution test from the finished drug product specifications is deemed acceptable.

B.12. BRIDGING OF PRODUCTS:

Assessment: Adequate

***Bridging of Formulations*:**

***Reviewer's assessment*:**

The oral solution is the final to-be-marketed (TBM) commercial formulation. The TBM drug product is proposed in a single (50 mg/mL) strength. The composition of the TBM formulation is shown below in Table 4.

Table 4: Composition of the TBM formulation

Material	% w/w	Quantity (mg/mL)	Function	Reference to Standards
Crinecerfont	(b) (4)	50.0[1]	Drug Substance	Module 3.2.S.4.1 in NDA 218808
Medium Chain Triglycerides (b) (4)		(b) (4)		Ph. Eur., USP/NF
				Ph. Eur., USP/NF
Butylated Hydroxytoluene				Ph. Eur., USP/NF
Saccharin				Ph. Eur., USP/NF
Orange Flavor (b) (4)				US FDA/ EU Food Grade[4]
Total Solution Weight	**100.0%**	(b) (4)		

[1] The dispensed amount of Crinecerfont (b) (4)

(b) (4)

Phase 1 (S# NBI-74788-1734) and Phase 3 (S# NBI-74788-CAH2006) studies were conducted on the final to-be-marketed (TBM) commercial formulation. Thus, bridging of formulations is not required. Assessment of the Phase 1 and Phase 3 studies is under the purview of the Clinical/Clinical Pharmacology Reviewers.

***Bridging of Manufacturing sites and Batch sizes*:**

***Reviewer's assessment*:**

A single site (b) (4) has been used to manufacture the TBM batches of the proposed drug product. Phase1 and Phase 3 studies were conducted on the drug product manufactured at (b) (4) Thus, bridging of manufacturing sites is not required.

The size of the Phase 1/Phase 3 batch manufactured at (b) (4) is (b) (4) (b) (4) The proposed commercial batch size for the drug product manufactured at (b) (4) is (b) (4) Thus, bridging of batch sizes is not required.

B.13. BIOWAIVER REQUEST:

Assessment: Adequate

***Reviewer's assessment*:**
Phase 1 and Phase 3 studies were conducted on the TBM product. The Applicant has not requested a waiver of bioavailability studies. The efficacy studies will be assessed by the Clinical/Clinical Pharmacology Reviewer.

R. REGIONAL INFORMATION:
Life Cycle Management Considerations and Risk Mitigation Strategies

***Reviewer's assessment*:**
The proposed drug product is an immediate-release product (b) (4) Based on the drug product being a true solution, the risk from a Biopharmaceutics perspective is low. Further risk mitigation is not required.

BIOPHARMACEUTICS PENDING DEFICIENCIES:
None

Rajesh Savkur

Digitally signed by Rajesh Savkur
Date: 9/05/2024 08:35:27PM
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Haritha Mandula

Digitally signed by Haritha Mandula
Date: 9/06/2024 05:50:18AM
GUID: 508da6fb000282df41459408f32a1ce0

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	A new molecular entity, is a selective corticotropin releasing factor 1 (CRF1) receptor antagonist [redacted] (b) (4)
NDA Number	218820
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Crinecerfont 50 mg/ml
Route of Administration	Oral solution
Applicant Name	Neurocrine Biosciences, Inc.
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DGE
Manufacturing Site	[redacted] (b) (4)
Method of Sterilization	N/A; the drug product is non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original submission	4/30/2024
Quality submission	6/18/2024
IR response	7/2/2024
Quality submission	8/7/2024
IR response	8/23/2024

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: None

Concise Description of Outstanding Issues: None

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Light yellow to orange non-aqueous solution

- **Drug product composition –**

Table 1: Composition of Crinecerfont Oral Solution, 50 mg/mL

Material	% w/w	Quantity (mg/mL)	Function	Reference to Standards
Crinecerfont	(b) (4)	50.0[1]	Drug Substance	Module 3.2.S.4.1 in NDA 218808
Medium Chain Triglycerides (b) (4)		(b) (4)		Ph. Eur., USP/NF
				Ph. Eur., USP/NF
Butylated Hydroxytoluene				Ph. Eur., USP/NF
Saccharin				Ph. Eur., USP/NF
Orange Flavor (b) (4)				US FDA/ EU Food Grade[4]
Total Solution Weight	**100.0%**	(b) (4)		

[1] The dispensed amount of Crinecerfont (b) (4)

(b) (4)

- **Description of container closure system –** 2 oz amber PET bottle and a 24 mm (b) (4) child-resistant induction-sealed cap

Exhibit batches: B230001, B230002 and B230003, (b) (4)

Proposed commercial batch: (b) (4)

Assessment: *Adequate*

The sponsor provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Assessment: ***Adequate***

The sponsor has met the regulatory expectations regarding the executed batch record.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

Store in refrigerator at 2-8ºC (36-46ºF); opened bottle can be stored at 15-25ºC (59-77ºF) for up to 30 days. Discard unused portion 30 days after first opening the bottle.

In-use study was performed for batch# B230001, B230002 (30 ml in 60 ml amber bottles) and B210065, B210067 (75 ml in 120 ml amber bottles) for 30 days (storage: 2-8ºC or 25ºC/65% RH, or 30ºC/65%). Results showed microbial limits test as well as *E.coli* test all met the stability specifications (3.2.P.8.3).

Assessment: *Adequate*

The package insert is acceptable.

MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date:
Jianli Xue, Ph.D.
CDER/OPQ/OPMA/DPMA IV
8/29/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya, Ph.D.
CDER/OPQ/OPMA/DPMA II
8/29/2024

Jianli Xue

Digitally signed by Jianli Xue
Date: 8/29/2024 09:20:05AM
GUID: 584afcd70041453da94854122880ab0c

Nandini Bhattacharya

Digitally signed by Nandini Bhattacharya
Date: 8/29/2024 09:27:38AM
GUID: 508da70c00028f454473851fced0e9d4

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/s/

AKM KHAIRUZZAMAN
10/07/2024 09:22:32 AM
The Office of Pharmaceutical Quality (OPQ) recommends an Approval on this NDA