CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761439Orig1/Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 146025

MEETING PRELIMINARY COMMENTS

Gedeon Richter Plc.
c/o Hikma Pharmaceuticals USA Inc
Attention: Amy Schutte
Senior Director, Regulatory Affairs
2 Esterbrook Lane
Cherry Hill, New Jersey 08003

Dear Amy Schutte:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RGB-14.

We also refer to your correspondence dated and received January 26, 2024, requesting a teleconference meeting to seek the Agency's concurrence on information to be submitted including technical content and format, to adequately support a BLA for RGB-14-P and RGB-14-X. The Sponsor would like to obtain the Agency's agreement that stability studies conducted are acceptable to support filing and review of the BLA and adequate to support the proposed expiration dating. The Sponsor would also like to gain alignment with the Agency on the planned presentation of the Integrated Summary of Immunogenicity (ISI) and summary of safety and efficacy to be included in the BLA, and to understand any drug product or device sampling that may be required in conjunction with the Agency's BLA review as well as discuss any potential concerns identified by the Agency.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at 301-796-2899.

Sincerely,

{See appended electronic signature page}

Noreen Cabellon, MS
Regulatory Project Manager
Endocrinology
Division of Regulatory Operations for Cardiology,
Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: Biological Product Development (BPD) Type 4

Meeting Date and Time: March 26, 2024, 10:00 to 11:00 AM EDT
Meeting Location: Teleconference

Application Number: IND 146025
Product Name: RGB-14 (Denosumab)

Indication: RGB-14 is being developed for the same indications as those approved for US-licensed Prolia (US-Prolia) and US licensed Xgeva (US-Xgeva)

Sponsor Name: Gedeon Richter, Plc.
Regulatory Pathway: 351(k) of the Public Health Service Act

FDA ATTENDEES (tentative)
Office of New Drugs (OND)/Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Division of General Endocrinology
Olivia Easley, MD, Clinical Reviewer
Shivangi Vachhani, MD, Clinical Team Lead
Naomi Lowy, MD, Deputy Director
Theresa Kehoe, MD, Director
Division of Pharm Tox for Cardiology, Hematology, Endocrinology, and Nephrology
Mekonnen Lemma Dechessa, PhD, Nonclinical Reviewer
Daniel Minck, PhD, Nonclinical Team Lead
David Carlson, PhD, Nonclinical Supervisor

Office of Translational Sciences (OTS)/Office of Clinical Pharmacology
Yaning Sun, PhD, Clinical Pharmacology Reviewer
Li Li, PhD, Clinical Pharmacology Team Lead

OTS/Office of Biostatistics
Mengjie Zheng, PhD, Biometrics Reviewer
Feng Li, PhD, Biometrics Team Leader

Office of Pharmaceutical Quality (OPQ)/Office of Product Quality Assessment
Hao Kiet Phan, PhD Product Quality Reviewer
Samuel Mindaye, PhD, Product Quality Team Leader
Leslie Ann Rivera Rosado, PhD, Review Chief
Joel Welch, PhD, Associate Director, Biosimilar Policy

OPQ, Office of Program and Regulatory Operations (OPRO)
Kristine Leahy, RPh Senior Regulatory Business Process Manager

Office of Surveillance and Epidemiology (OSE)/ Office of Medication Error Prevention and Risk Management
Division of Risk Management
Theresa Ng, PharmD, Senior Risk Management Analyst
Yasmeen Abou-Sayed, PharmD, RPh, Team Lead

OSE/Immediate Office/Project Management Staff
Deveonne Hamilton-Stokes, RN, BSN, MA, Safety Regulatory Project Manager
Nichelle Rashid, MS, Team Lead, Project Management Staff
Ameet Joshi, PharmD, RPh, Team Lead, Project Management Staff

Office of Therapeutic Biologics and Biosimilars
Sabiha Khan, M.D., Scientific Reviewer
Nina Brahme, Ph.D., M.P.H., Scientific Reviewer
Emanuela Lacana, PhD, Deputy Director
Chau Nguyen, PharmD, Project Manager
Wendy Streight, Ph.D., Senior Project Manager
Christine Kim, PharmD, RAC-US, Senior Project Manager
Jacquelyn Rosenberger, PharmD, RAC, Senior Project Manager

OND/Office of Oncologic Diseases (OOD)
Division of Oncology I
Gwynn Ison, MD, Clinical Reviewer
Division of Oncology II
Diana Bradford, MD, Clinical Reviewer
Division of Hematology Malignancies II
Bindu Kanapuru, MD, Clinical Reviewer

Office of the Commissioner (OC)/Office of Clinical Policy and Programs (OCPP)/Office of Combination Products (OCP)
Bindi Nikhar, MD, Associate Clinical Director

Office of Compliance/Office of Scientific Investigations
Division of Clinical Compliance Evaluation
Ling Yang, MD, PhD, Medical Officer
Min Lu, MD, MPH, Team Lead

OND/Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Noreen Cabellon, MS, Regulatory Project Manager
Julie Van der Waag, MPH, Director

SPONSOR ATTENDEES

Name	Title	Company/Discipline
Chiara Moro	Senior Global Regulatory Lead	Gedeon Richter/Regulatory Affairs
László Tóth	Head of Biotechnology Process Development and Analytics	Gedeon Richter/CMC Development
Bálint Gyurácz	Senior CMC Project Manager	Gedeon Richter/CMC Development
Joachim Kiefer	Head of Biotechnology Clinical Department	Gedeon Richter/Clinical Development
Rania Abdulahad	Senior R&D Program Manager	Gedeon Richter/ Project Management
Klemen Spaninger	Head of Biotechnology Project Management	Gedeon Richter/ Project Management
Parag Goyal	Head of Biosimilar Development	Hikma/R&D
Tae Kim	Director, Clinical	Hikma/R&D
Amy Schutte	Senior Director, Regulatory Affairs	Hikma/Regulatory Affairs
Kathleen Zassick	Manager, Regulatory Affairs	Hikma/Regulatory Affairs
Amar Jain	Senior Project Manager	Hikma/Project Management

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 26, 2024, 10:00 to 11:00 AM EDT between Gedeon Richter, Plc. and the Division of General Endocrinology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Gedeon Richter Plc. (Gedeon) is developing RGB-14-P and RGB-14-X as proposed biosimilar products to US-Prolia and US-Xgeva, respectively.

An initial BPD Type 2 meeting with Gedeon to discuss the quality, nonclinical, and clinical development plans for RGB-14-P and RGB-14-X was held on December 20, 2019, and meeting minutes were issued on January 17, 2020. Written responses were issued for a subsequent BPD Type 2 meeting request which addressed Gedeon's questions relating to the forced degradation study plan of the methods and stress conditions, the omission of the single transition and the subsequent open-label extension phase in the comparative efficacy/safety study, and the adequacy of the data generated via a human factor study by (b) (4) in relation to the safety needle guard to be used for the proposed RGB-14-P device on October 16, 2020.

On April 6, 2021, Gedeon submitted their IND application. Subsequently, on May 5, 2021, the IND was placed on full clinical hold via teleconference between FDA and Gedeon. During this teleconference, FDA notified Gedeon that their device constituent parts were not safe for use. Because there were multiple 510k configurations with differences in design and performance, FDA requested the submission of the sponsor's design for verification testing. Gedeon submitted their clinical hold response on August 6, 2021, and the full clinical hold was removed on September 3, 2021. Written responses for a third BPD Type 2 meeting request were issued on October 19, 2022, to discuss the approach that the measured quality parameters, the listed analytical methods, and the five stress conditions applied in the head-to-head forced degradation study (as outlined in the Forced Degradation Study Protocol) were adequate to support the comparative analytical assessment.

A BPD Type 2b meeting with Gedeon was held on July 19, 2023, to discuss the development of the device component of the combination product. Specifically, Gedeon requested concurrence on the selection of Essential Performance Requirements (EPRs), primary function of the device parts, control strategy, and the sampling methodology for design verification. Gedeon also requested feedback on the control strategy for the high and low molecular weight species, process related impurities, extractable and leachable risk assessment, and shipping validation strategy for cold chain product RGB-14-P. Meeting minutes were issued on July 26, 2023.

On January 26, 2024, Gedeon requested this BPD Type 4 meeting to seek the Agency's concurrence on information to be submitted including technical content and format, to adequately support a BLA for RGB-14-P and RGB-14-X. Gedeon would like to obtain the Agency's agreement that stability studies conducted are acceptable to support filing and review of the BLA and adequate to support the proposed expiration dating. Gedeon would also like to gain alignment with the Agency on the planned presentation of the Integrated Summary of Immunogenicity (ISI) and summary of safety and efficacy to be included in the BLA, and to understand any drug product or device

sampling that may be required in conjunction with the Agency's BLA review as well as discuss any potential concerns identified by the Agency.

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Gedeon Richter, Plc. and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2.0 DISCUSSION

Sponsor's questions are repeated below followed by FDA's response in **bold**.

2.1. Chemistry, Manufacturing, and Control (CMC)

Question 1: Does the Agency agree with the proposed content and placement of information in support a 351(k) BLA for RGB-14-X and RGB-14-P considered complete and will enable the Agency's acceptance of the application for filing and review?

FDA Response to Question 1:
The overall content and placement of information in the future 351(k) BLA for RGB-14-X and RGB-14-P is acceptable for filing and review. We have following recommendations:

1. **In Module 2.5 Introduction, discuss the data and information that supports extrapolation and licensure for each of the indications being sought and for which US-Prolia and US-Xgeva have previously been approved.**

2. **We recommend you submit your clinical study report for RGB-14-001 (pharmacokinetic similarity study) in Module 5.3.3.**

3. **For both studies RGB-14-001[1] and RGB-14-101[2] submit narratives and case report forms for serious adverse events and adverse events leading to premature discontinuation. These can be included in the respective study reports in Modules 5.3.3 and 5.3.5.1**

4. **We agree with your approach to the proposed REMS and consider a REMS consisting of the REMS Document, REMS materials, and REMS Supporting Document to be adequate for the initial BLA. However, please note the**

[1] Study RGB-14-001: Randomized, double-blind, single, 60 mg fixed dose, parallel comparative pharmacokinetic and pharmacodynamic study of RGB-14 and US-sourced Xgeva in healthy adult male subjects
[2] Study RGB-14-101: Randomized, double-blind, multicenter phase 3 study to assess the efficacy and safety of RGB-14-P compared to US-sourced Prolia in women with postmenopausal osteoporosis

recently approved modification on March 5, 2024, to the Prolia REMS and align your REMS proposal with the recent changes. (See updates on REMS@FDA.)

5. **To facilitate the Agency's assessment of the control strategy for RGB-14-X and RGB-14-P drug substance and drug product manufacturing process, provide the information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation in the tabular format as provided in the Additional Comments section.**

Question 2: Does the Agency agree that the stability data planned for inclusion in Section 3.2.P.8.3 of the BLA is appropriate to support the BLA filing and a proposed 36-month expiration dating?

FDA Response to Question 2:
The stability data planned for inclusion in Section 3.2.P.8.3 of the BLA are adequate to support the BLA filing. However, it is premature to agree to a shelf life for RGB-14-X and RGB-14-P. In general, expiration dates will be determined following review of the overall stability data as well as analytical comparability data submitted to support changes implemented during product development.

Question 3: In conjunction with its review of the BLA for RGB-14-X and RGB-14-P will the Agency request drug product or device samples? If so, it would be beneficial to the Sponsor to understand the number of samples, sample type, and any lot number requirements for planning purposes due to the complexity of international shipment.

FDA Response to Question 3:
No, the Agency will not seek drug product or device samples in conjunction with review of this BLA.

2.2. Clinical

Question 4: Does the Agency agree with the structure of the dossier with regard to the Integrated Summary of Immunogenicity (ISI) in Module 5.3.5.3 with corresponding summary in Module 2.7.2.4 and summaries of safety and efficacy in Module 2.5?

FDA Response to Question 4:
Yes, the structure is acceptable with the Integrated Summary of Immunogenicity in Module 5.3.5.3 with the corresponding summaries as proposed.

Additional Comments:

Combination Product

1. **As acknowledged in the briefing package, the proposed RGB-14-P/60 mg denosumab biosimilar provided in a prefilled syringe with (b) (4) (b) (4) Needle Guard is a combination product per 21 CFR 3.2(e)(1). Please note that Part 3 combination products are subject to 21 CFR Part 4.A "Current Good Manufacturing Practice Requirements for Combination Products"[3]. Please also refer to FDA's guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products.*[4]**

2. **In your future IND submission, Form 1571 should identify your product as a combination product (see form field 13). In your future BLA submission, Form 356h should identify your product as a combination product (see form field 24); the combination product Type will depend on the final to-be-marketed configuration. Also, identify all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.**

3. **For information on the location of device related information, see Section 5 of the Agency eCTD Technical Conformance Guide: Technical Specifications Document[5] and FDA's guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.**

4. **Part 3 combination products are subject to post-market reporting safety requirements per 21 CFR Part 4.B. For more information on post-market safety reporting requirements for combination products, see FDA's website.[6]**

5. **Clarify whether the comparative efficacy and safety study in patients with postmenopausal osteoporosis (Study RGB-14-101) was conducted with the to-be-marketed (TBM) combination product (i.e., prefilled syringe with (b) (4) Needle Guard). If the TBM combination product was not used, clarify which product was used.**

---

[3] Accessible at: https://www.federalregister.gov/documents/2017/01/11/2017-00411/current-good-manufacturing-practice-requirements-for-combination-products-guidance-for-industry-and

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[5] Accessible at: https://www.fda.gov/media/93818/download

[6] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

CMC

To facilitate the Agency's assessment of information in your future BLA, please provide the information as requested below. The requested information should summarize information from Module 3 and may be submitted either to Module 1 or Module 3.2.R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

6. **To facilitate the Agency's assessment of the RGB-14-X and RGB-14-P drug substance (DS) and drug product (DP) manufacturing process, provide the information for each process parameter and in-process control, as applicable, in the tabular format provided below. Please provide a separate table for each unit operation indicated in RGB-14-X and RGB-14-P DS section 3.2.S.2.2 and for each unit operation of the manufacturing process for the DP section 3.2.P.3.3. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3.2.R.**

Process parameter/ critical process parameter/potential critical process parameter/ in-process control (IPC)	Proven Acceptable Range/ Normal Acceptable Range/ Control limits/Targets[1] for commercial manufacturing process	Criticality classification[2]	Characterized Range/ Control limits/Targets[1] from process development studies	Manufactured Range/ Control limits/Targets[1] from pivotal study lots	Manufactured Range/ Control limits/Targets[1] from process validation
[1]As applicable. [2]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.					

7. **To facilitate the Agency's assessment of the control strategy for RGB-14-X and RGB-14-P, provide information for quality attributes and process and product related impurities for the RGB-14-X and RGB-14-P DP in the following tabular format. Provide a separate table for the DS and DP. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3.2.R.**

Critical Quality Attributes (including Process and Product related impurities for DS and DP)	Criticality classification	Impact[1]	Source[2]	Analytical method [3]	Proposed control strategy[4]
[1]What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy. [2]What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column. [3]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.					

[4]List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.

8. To facilitate the Agency's assessment of the adequacy of the proposed commercial release specifications of RGB-14-X and RGB-14-P DS and DP, provide information for each release specification in the tabular format provided below. Please provide a separate table for RGB-14-X and RGB-14-P DS, and DP, as described below. Each release specification should be described in a separate row. Add additional rows for additional release specifications, as needed. In general, include footnotes for each column of grouped results to indicate which lot numbers were used for each calculation of minimum-maximum range, and provide the number of batches or lots used (n=?) in the table as well.

Release Specification for RGB-14-X and RGB-14-P Drug Substance							
Attribute	Analytical method	Proposed commercial release acceptance criteria	Release results for non-GMP DS batches[1] (n=?) (min-max)	Release results for non-PPQ GMP clinical DS batches using the clinical manufacturing process[2] (n=?) (min-max)	Release results for non-PPQ GMP clinical DS batches using to-be-marketed manufacturing process[3] (n=?) (min-max)	Release results for DS PPQ batches[4] (n=?) (min-max)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

[1]List all non-GMP DS batches included in the range calculation.
[2]List all non-PPQ GMP clinical DS batches using the clinical process included in the range calculation.
[3]List all non-PPQ GMP clinical DS batches using the to-be-marketed process included in the range calculation.
[4]List all PPQ DS batches included in the range calculation.

Release Specification for RGB-14-X and RGB-14-P Drug Product							
Attribute	Analytical method	Proposed commercial release acceptance criteria	Release results for non-clinical and developmental DP lots[1] (n=?) (min-max)	Release results for non-PPQ clinical DP lots using clinical formulation[2] (n=?) (min-max)	Release results for non-PPQ clinical DP lots using to-be-marketed formulation[3] (n=?) (min-max)	Release results for DP PPQ lots[4] (n=?) (min-max)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

[1]List all non-clinical and developmental DP lots included in the range calculation.
[2]List all non-PPQ clinical DP lots using clinical formulation included in the range calculation.
[3]List all non-PPQ clinical DP lots using to-be-marketed formulation included in the range calculation.
[4]List all PPQ DP lots included in the range calculation.

9. To facilitate the Agency's assessment of the adequacy of the stability specifications of RGB-14-X and RGB-14-P DS and DP, provide stability information for storage at recommended condition for each stability specification in the tabular format provided below. Please provide a separate table for DS and DP, as described below. Each stability specification should be described in a separate row. Add additional rows for additional stability specifications, as needed. If any stability specifications are different than the corresponding release specification for an analytical method that is used for both, then provide justification why different acceptance criteria are proposed for release and stability. Include footnotes to the tables to list the batch numbers that were used in each assessment. Consider the data from all stability time points, not only release and end of proposed shelf-life. If a batch or lot has not completed stability testing to the end of the proposed shelf-life, include data from all time points that are currently available for that batch or lot in the evaluation.

Stability Specification for RGB-14-X and RGB-14-P Drug Substance[1]				
Attribute	Analytical Method	Stability acceptance criteria	Stability results for batches stored at -70±10°C (n=?) Min – Max (Range for all data from time 0 to the longest currently available time point or 36 months)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)
[1]List each of the batch numbers, with the corresponding batch age, included in the range calculations.				

Stability Specification for RGB-14-X and RGB-14-P Drug Product[1]				
Attribute	Analytical Method	Stability acceptance criteria	Stability results for batches stored at 2-8°C (n=?) Min – Max (Range for all data from time 0 to the longest currently available time point or 24 months)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)
[1]List each of the lot numbers, with the corresponding lot age, included in the range calculations.				

10. To facilitate the Agency's assessment of the comparability between lots used in clinical studies and those produced using the proposed commercial process, provide comparative information for each manufacturing process step, extended characterization testing, release testing, real time, accelerated and temperature stress stability results, and forced degradation results for the RGB-14-X and RGB-14-P DS and DP in the following tabular format. Provide a separate table for DS and DP. Add additional columns for additional manufacturing processes used. Add additional rows as needed. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3.2.R.

Comparison of Manufacturing Processes Used During Development		
	Process <description>	Process <description>
Manufacturing Site		
Cell Bank/DS Process/DP Process Used[1]		
Fermentation Scale/Batch Size[1]		
Manufacturing Process Step 1[2]		
Manufacturing Process Step 2...[2]		
[1]As applicable [2]For example Seed expansion, production bioreactor, harvest, Protein A capture, etc. Describe each manufacturing step in a separate row. Add additional rows as needed. All differences between the processes should be indicated in the table.		

Comparison of Release Test Results						
	Process <description>			Process <description>		
Release Test Method[1]	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>
Method 1	(result)					
Method 2...						
[1]Each release test method should be described in a separate row.						

Comparison of Extended Characterization Results						
	Process <description>			Process <description>		
Extended Characterization Test Method[1]	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>
Method 1	(result)					
Method 2...						
[1]Each extended characterization test method should be described in a separate row.						

Comparison of Stability Results at Recommended Storage Condition							
		Process <description>			Process <description>		
		Result at time 0 and at the proposed end of shelf life (or latest available time point)					
Stability Test Method[1]	Storage duration (months)	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>
Method 1							
Method 2...							
[1]Each stability test method should be described in a separate row.							

Comparison of Stability Results under Accelerated Storage Conditions							
Accelerated stability condition[1]							
		Process <description>			Process <description>		
		Result at time 0 and end of study (or latest available time point)					
Stability Test Methods[2]	Storage duration (months)	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>
Method 1							
Method 2...							
[1]Provide a separate table for each accelerated stability storage condition tested. [2]Each stability test method should be described in a separate row.							

Comparison of Stability Results under Stressed Storage or Forced Degradation Conditions							
Stressed storage condition[1]							
		Process <description>			Process <description>		
		Range of results from time 0 to last time point studied					
Stability Test Methods[2]	Storage duration (months)	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>	Lot <number>
Method 1							
Method 2...							
[1]Provide a separate table for each stress stability condition tested. [2]Each stability test method should be described in a separate row.							

11. To facilitate the Agency's assessment of the suitability of the analytical methods for release and stability testing of RGB-14-P pre-filled syringe

(PFS), and for in-process test methods, provide summarized results of method validation in the tabular format provided below. Please provide a separate table for each analytical method, as described below. Each parameter, e.g. specificity, precision, accuracy, etc. should be described in a separate row. Add additional rows for additional parameters, as needed. Study design should include a brief description of the testing material (batch information), the number of tests (e.g., the number of replicates, runs, plates, analysts, etc., if applicable), design of the experiment, approach of data reporting, and other important overview information regarding the validation of that parameter, as needed. Indicate in the table title the name of the method and all applicable programs where it is used such as DS release/stability, DP PFS release/stability, or in-process testing.

Summary of Validation Results for Method 1 (used for DS release/stability, in-process testing, etc.)			
Location of testing site:	Location where method was validated:		
System Suitability Acceptance Criteria:			
Description of lots used (e.g. material, manufacturing process, formulation, and concentration):			
Parameter	Study Design	Acceptance Criteria	Validation Results

12. Provide the following RGB-14-X and RGB-14-P DS batch information and the corresponding DP lot information made from the DS batch in your biologics license application. Add additional rows as needed. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3.2.R.:

Manufacturing and Pharmaceutical Development DS Batch and DP Lot List								
RGB-14-X/RGB-14-P DS				RGB-14-X/RGB-14-P DP				Purpose
Parent Batch Number[1]	Manufacturing Scale	Date of Manufacturing	Manufacturing Site	Lot Number[2,3]	Presentation and Formulation	Date of Manufacturing	Manufacturing Site	

[1]Footnote if the DS batch was used in the process performance qualification (PPQ) study and the associated PPQ number
[2]Footnote if the DP lot was used in the PPQ study and the associated PPQ number
[3]If multiple DS batches were used in the manufacture of a DP lot, note the other contributing parent DS batch number(s) in parenthesis.

13. Provide the following drug master file information referenced in your biologics license application:

DMF #	DMF Type	DMF Holder	Item referenced	Link to Letter of Cross-Reference	Comments

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA III. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[7]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing,

[7] https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For additional information on how you may fulfill the requirement for pediatric assessments or investigations under PREA, see question and answer I.16 in the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act*.

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[8]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed Prescribing Information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d)[9] and

[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended

[9] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

201.57[10] including the Pregnancy and Lactation Labeling Rule (PLLR). As you develop your proposed PI, we encourage you to review the labeling review resources on the following websites:

- *Biological Products – Specific Labeling Resources*[11] which includes the guidance for industry*: Labeling for Biosimilar Products* (July 2018).
- *Prescribing Information Resources*[12]

For other prescription drug labeling resources such as those for FDA-approved patient labeling, carton and container labeling, labeling databases, and product databases, visit *FDA's Labeling Resources for Human Prescription Drugs* website.[13]

- Pursuant to the PLLR, you should include the following information with your application to support the changes in the *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential* subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.[14]

Prior to submission of your proposed PI, use the Selected Requirements for Prescribing Information (SRPI) checklist to ensure conformance with the format items in regulations and guidances.

---

[10] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[11] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources

[12] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources

[13] https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

[14] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

MANUFACTURING FACILITIES

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the CGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection, 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to facilitate planning of pre-license inspections during the review cycle. For a BLA submission, when providing the preliminary manufacturing schedule, we encourage you to bear in mind the anticipated time frame for the late-cycle meeting for applications subject to "the Program" under BSUFA III.

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[15] and the guidance for industry, *Identification of Manufacturing Establishments in*

[15] https://www.fda.gov/media/84223/download

Applications Submitted to CBER and CDER Questions and Answers[16]*.* Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.

RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS

If you are planning to include a clinical pharmacology study as part of your 351(k) BLA marketing application, we have the following general best practice recommendations for you to keep in mind as you prepare your submission, including guides for formatting your submission.

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:

    a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).

    b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable,

[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

for the studies included in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).

c. Present the PK (and PD, when applicable) parameter data as geometric mean with coefficient of variation, mean ± standard deviation, and median with range in the study reports and throughout the BLA.

d. Provide analysis data sets for all concentration-time and derived PK (and PD, when applicable) parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

2. Include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:

   a. Site number

   b. Principal investigator

   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

3. Submit all PK (and PD, when applicable) bioanalytical method validation reports and bioanalytical study reports. In addition, complete the summary tables using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document[17] to provide the information regarding the bioanalytical methods for pharmacokinetic and/or biomarker assessments used in clinical pharmacology studies and their life-cycle information pertaining to the studies. Submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

[17] https://www.fda.gov/media/131425/download

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/

NOREEN N CABELLON
03/22/2024 01:06:08 PM