CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761444Orig1s000
761444Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 153872

MEETING PRELIMINARY COMMENTS

Shanghai Henlius Biotech, Inc.
c/o Henlius USA Inc.
Attention: Xiaofang Jin, M.S
Associate Director
430 N. McCarthy Blvd
Milpitas, CA 95035

Dear Xiaofang Jin:

Please refer to your pre-investigational new drug application (PIND) file for HLX14.

We also refer to your April 16, 2024, correspondence requesting a meeting to discuss and obtain the Agency's agreement on the proposed BLA data package and the marketing filing strategy for HLX14.

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, contact me at Noreen.Cabellon@fda.hhs.gov or 301-796-2899.

Sincerely,

{See appended electronic signature page}

Noreen Cabellon, MS
Senior 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:
Meeting Preliminary Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Reference ID: 5896202

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: June 14, 2024, 9:00 AM to 10:00 AM EDT
Meeting Location: Teleconference

Application Number: PIND 153872
Product Name: HLX14
Indication: HLX14 is being developed for the same indications as those approved for US-licensed Prolia and US-licensed Xgeva
Sponsor Name: Shanghai Henlius Biotech, Inc.
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
Feleke Eshete, PhD, Nonclinical Reviewer
David Carlson, PhD, Nonclinical Supervisor

Office of Translational Sciences (OTS)/Office of Clinical Pharmacology
Po-Hung Hsieh, PhD, Clinical Pharmacology Reviewer
Li Li, PhD, Clinical Pharmacology Team Lead

OTS/Office of Biostatistics
Alexander Cambon, PhD, Biometrics Reviewer
Feng Li, PhD, Biometrics Team Lead

Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products
Samuel Mindaye, Ph.D., Product Quality Team Lead
Gunther Boekhoudt, Ph.D., Product Quality Assessor
Joel Welch, PhD, Associate Director, Biosimilar Policy

Office of Surveillance and Epidemiology (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

OSE/Office of Medication Error Prevention and Risk Management
Division of Risk Management
Theresa Ng, PharmD, Risk Management Analyst
Yasmeen Abou-Sayed, PharmD, Team Leader
Division of Medication Error Prevention and Analysis (DMEPA)
Melina Fanari, RPh, Safety Evaluator

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 Therapeutic Biologics and Biosimilars
Nina Brahme, Ph.D., MPH, Scientific Reviewer
Frances Andrada, MSN, CRNP, FNP-BC, CNRN, Scientific Reviewer
Emanuela Lacana, PhD, Deputy Director
Wendy Streight, Ph.D., Senior Regulatory Project Manager
Christine Kim, PharmD, RAC-US, Senior Regulatory Project Manager
Jacquelyn Rosenberger, PharmD, RAC, Senior Regulatory Project Manager

OND/Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Noreen Cabellon, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES

Name	**Title**
Chen Ma	Sr. Director, Global Quality Operations, Henlius
Ping Han	Sr. Director, Analytical Sciences and Development, Henlius
Peilan Qin	Sr. Manager, Analytical Sciences and Development, Henlius
Yuan Fang	Director, Drug Product Development, Henlius
Lu Dai	Manager, Drug Product Development, Henlius
Qiuli Hu	Associate Director, Quality Control, Henlius
Guolin Sun	Project Supervisor, Quality Control, Henlius
Bin Gao	Senior Manager, CMC Operation, Henlius
Qingyu Wang	Deputy General Manager, Medical, Henlius
Liang Zhou	Sr. Director, Clinical PK/PD, Henlius
Mengkai Chen	Associate Director, Biostatistics, Henlius
Bei Gong	Sr. Manager, Pharmacovigilance, Henlius
Xiaoling Yuan	Director, Preclinical Development, Henlius
Jin Li	General Manager, Regulatory Affairs, Henlius

Xuejiao Sun	Director, Regulatory Affairs, Henlius
Xiaofang Jin	Associate Director, Regulatory Affairs, Henlius
Alok Gokhale	Sr. Scientist, Global Regulatory Affairs, Organon
Preena Modi	Director, Regulatory Affairs-CMC, Organon
	(b) (4)

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 June 14, 2024, 9:00 AM to 10:00 AM EDT between Shanghai Henlius Biotech, Inc. 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the 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

Shanghai Henlius Biotech, Inc. (Henlius) is developing HLX14-P and HLX14-X as biosimilar to US-licensed Prolia (US-Prolia) and US-licensed Xgeva (US-Xgeva), respectively, and is seeking the same indications as those approved for US-Prolia and US-Xgeva.

An initial BPD Type 2 meeting with Henlius to discuss to discuss CMC, clinical, and nonclinical aspects for product development of HLX14 was granted on December 14, 2020. The sponsor requested cancellation of the meeting following receipt of the preliminary comments issued on February 18, 2021.

A BPD Type 2b meeting was held on February 23, 2023, to discuss and obtain feedback on the analytical similarity plan, and the device and human factor study plan for the PFS presentation of the HLX14-P product. In a post-meeting comment, FDA committed to providing a written response to the sponsor's URRA and any specific questions within 60 days. FDA issued the sponsor a response to their January 24, 2024, URRA proposal on March 13, 2024.

On April 4, 2024, FDA granted a BPD Type 2a meeting, to discuss and seek agreement on the data adequacy of the following: the proposed (b) (4) (b) (4) could support HLX14 biosimilar licensure; and the proposed microbial related control strategy and environmental monitoring plan is sufficient for use in a routine GMP commercial manufacturing environment. The meeting was held on May 17, 2024.

Henlius requested this BPD Type 4 meeting to discuss and obtain the Agency's agreement on the proposed BLA data package and the marketing filing strategy for HLX14. The meeting package was received on April 29, 2024.

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 Shanghai Henlius Biotech, Inc. 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

Your questions are repeated below with our responses followed in **bold**.

2.1. Chemistry, Manufacturing, and Controls

Question 1: Does the Agency agree that the stability data available at the initial submission is sufficient to support the initial BLA filing and updated stability data can be submitted during review period?

FDA Response to Question 1:
The proposed stability data at the initial submission as described in Table 32 of the meeting package appears reasonable. Regarding the proposal to submit stability data update during the review, you may provide a "simple stability update" to support your proposed dating period for drug substance and drug product. Simple stability update consists of stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or

bracketing approaches which deviate from the stability protocol in the original BLA. Simple stability updates submitted up to month 7 for a standard submission will be reviewed and considered in shelf-life determination. The overall adequacy of the stability study data will be a review issue based on the totality of information and data presented in the BLA submissions.

2.2. Non-Clinical

Question 2: Given the similarity of HLX14 and the reference products (Prolia and XGEVA) has been demonstrated in comprehensive analytical studies, clinical PK similarity study (HLX14-001) and comparative clinical study (HLX14-002-PMOP), does the Agency agree that non-clinical animal studies (Module 4) and non-clinical written and tabulated summaries (Module 2.6) are not needed, and the proposed nonclinical overview (Module 2.4) with justification is sufficient to support the BLA from the non-clinical perspective?

FDA Response to Question 2:
We agree that if you do not intend to support your demonstration of biosimilarity with nonclinical studies and you have no study reports to include in Module 4 or Module 2.6, it is appropriate to limit your nonclinical discussion and justification to a Nonclinical Overview in Module 2.4.

2.3. Clinical

General comments:

1. **Include an explanation for how the submitted data and information support that HLX14 can be expected to produce the same clinical result as the reference product in any given patient and that for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. For more information, see guidance for industry *Considerations in Demonstrating Interchangeability with a Reference Product*.[1]**

2. **Many factors, including nutritional factors, which may vary between populations, can impact bone health. Therefore, the sensitivity of the clinical study may vary between geographic populations. Given that a non-US population was enrolled in your comparative clinical study, provide a discussion and any relevant data addressing whether the bone mineral**

[1] 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.

density (BMD) response to the study drugs was similar to the BMD response observed in prior efficacy studies of the reference product.

Question 3: Given there is only one clinical study with efficacy data, i.e., the Phase III comparative clinical study HLX14-002-PMOP301, the sponsor does not intend to include an Integrated Summary of Efficacy (ISE) in the planned BLA. Does the Agency agree with the Summary of Clinical Efficacy (Module 2.7.3) is adequate to fulfill the requirements for the ISE?

FDA Response to Question 3: **Yes. An ISE is not required, and a Summary of Clinical Efficacy (SCE) is adequate.**

For the efficacy and safety datasets from the comparative clinical study, please ensure that subject ID numbers are consistent across treatment periods.

Question 4: Given the study populations are distinct in the 2 clinical studies, Phase I PK similarity study in healthy volunteer and Phase 3 comparative clinical study in postmenopausal women with osteoporosis at high risk of fracture, the sponsor does not intend to include an Integrated Summary of Safety (ISS) in the planned BLA. Does the Agency agree with the Summary of Clinical Safety (Module 2.7.4) can be sufficiently detailed to fulfill the requirement for the ISS?

FDA Response to Question 4: **Yes. The Summary of Clinical Safety (SCS) can stand in lieu of an ISS. Please include an integrated summary of immunogenicity where immunogenicity results from the comparative PK study and the comparative clinical study in post-menopausal women are addressed. This summary can be located in Module 5.3.5.3.**

Question 5: Does the Agency agree with the proposed criteria for inclusion of patient narratives and CRFs in the BLA submission?

FDA Response to Question 5: **Yes. Inclusion of patient narratives and CRFs for deaths, serious adverse events, and premature discontinuations due to adverse events (regardless of relatedness) is acceptable.**

2.4. Regulatory

Question 6: Does the Agency concur that one single BLA package is sufficient to support the review and marketing approval for HLX14 60 mg and HLX14 120 mg with the different proprietary names?

FDA Response to Question 6:
A single 351(k) BLA submission for the two product presentations with separate labeling based on the proposed indications may be acceptable if

sufficient data and information are included in the original application to support a demonstration that HLX14 is biosimilar to US-Prolia and US-Xgeva. Licensure for the same indications approved for US-Prolia and US-Xgeva may be possible if adequate scientific justification to support extrapolation is provided.

With respect to the proprietary names, we find your approach of having different proprietary names to be reasonable. However, please note that the acceptability of a dual proprietary name will be a review issue. Note that you will need to submit each of your proposed proprietary names separately.

Follow the procedure below to ensure that the document room accurately codes for a "Proprietary Name/Request for Review" and opens an OSE PDUFA clock for the BLA name reviews.

When submitting a proprietary name request for review to the Agency, it is crucial to:

- **Check "Request for Proprietary Name Review" in Box 21 of FDA form 356h.**
- **Include the statement "REQUEST FOR PROPRIETARY NAME REVIEW" in bold capital letters, at the top of your cover letter and at the top of the first page of the main submission document (refer to the complete submission guidance link below).**
- **Clearly state in the cover letter and supporting documentation the exact name you are requesting for review and include the phonetic spelling of the name.**
- **If you have already submitted draft labels & labeling, please add a link to them in the cover letter.**

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- **Guidance for Industry: *Contents of a Complete Submission for the Evaluation of Proprietary Names***
- ***PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*[2]**

[2] https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf

Question 7: Does the Agency agree with the proposed content and format for the BLA as described below?

FDA Response to Question 7: **Yes, the proposed content and format of the BLA is acceptable.**

Additional FDA Comments

Device content for marketing application
Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: Guidance for Industry *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*[3].

When submitting a marketing application for the final finished combination product, provide the following information related to your device:

1. **Device Description Documentation**
    a. **Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.**

    b. **Describe the principles of operation of your device.**

    c. **Describe any accessories or other devices labeled for use with your device.**

2. **Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the FDA Design Control Guidance for Medical Device Manufacturers[4], We recommend that the design control information provided in your application include the following:**

    a. **Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)**

[3] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf
[4] https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf.

b. **Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)**

c. **Design Verification Plan/Summary Report, supporting data and traceability**

d. **Design Validation Plan/Summary Report, supporting data and traceability**

e. **Risk Management File**

3. **Essential Performance – Identify essential performance requirements (EPR) for the device.**

   For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. While the final set of essential performance requirements should be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors should influence your EPR selection.

   Example prefilled syringe EPRs:
   a. **Delivered Volume Accuracy**
   b. **Break loose & Extrusion Force**

   Example needle safety primary functions
   c. **Needle Safety Activation Force**
   d. **Needle Safety Override Force**

   Please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*

4. **Stability (ICH Q1) – Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.**

5. **Shipping - Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.**

6. **Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot**

release, in-process, control of incoming materials, purchasing controls, etc.

7. **Quality System - The marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: *Current Good Manufacturing Practice Requirements for Combination Products.***

8. **Considerations specific to your device constituent**

    a. **Needle Safety – Provide documentation to support the needle safety performance of your combination product to a sufficient reliability and up to its proposed shelf-life per ISO 23908:2011 Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling. Malfunction of the needle safety may lead to accidental needle sticks and transmission of bloodborne pathogens. Therefore, ensure the provided testing is performed after pre-conditioning representative of intended use (e.g., shipping, drop) and to a reliability commensurate with the risk (e.g., 99% reliability).**

Risk Evaluation and Mitigation Strategy

9. **We remind you there is currently an approved REMS for US-Prolia. HLX14 will need to be submitted with a proposed REMS that contains the same REMS elements to inform healthcare providers and patients about specific risks as currently available for Prolia. (See REMS@FDA for the latest changes to the approved Prolia REMS on March 5, 2024.)**

Combination Product

10. **The proposed HLX-14 product that will be provided in a prefilled syringe is a single-entity 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"[5]. Please also refer to FDA's guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products***

11. **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 is Type 2. Also, identify all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent**

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

part and all facilities responsible for the disposition (e.g., release) of the combination product.

12. **For information on the location of device related information, see Section 5 of the Agency eCTD Technical Conformance Guide: Technical Specifications Document[6] and FDA's guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.**

13. **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[7].**

Product Quality

To facilitate the Agency's assessment of your future BLA submission, 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.

14. **To facilitate the Agency's assessment of the HLX14 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 HLX14 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.**

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.					

[6] https://www.fda.gov/media/93818/download
[7] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

[2]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.

15. To facilitate the Agency's assessment of the control strategy for HLX14, provide information for quality attributes and process and product related impurities for the HLX14 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.

16. To facilitate the Agency's assessment of the adequacy of the proposed commercial release specifications of HLX14 DS and DP, provide information for each release specification in the tabular format provided below. Please provide a separate table for HLX14 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 HLX14 Drug Substance							
Attribute	Analytical method	Proposed commercial release acceptance	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]	Release results for non-PPQ GMP clinical DS batches using to-be-marketed manufacturin	Release results for DS PPQ batches[4] (n=?) (min-max)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

		criteria		(n=?) (min-max)	g process[3] (n=?) (min-max)		

[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 HLX14 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.

17. To facilitate the Agency's assessment of the adequacy of the stability specifications of HLX14 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 HLX14 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 HLX14 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.				

18. 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 HLX14 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.							

19. To facilitate the Agency's assessment of the suitability of the analytical methods for release and stability testing of HLX14 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

20. Provide the following HLX14 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								
HLX14 DS				HLX14 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.

21. 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 INFORAMTION

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.[8]

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, 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.

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

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*[9]. 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)[10] and 201.57[11] 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*[12] which includes the guidance for industry*: Labeling for Biosimilar Products* (July 2018).

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[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] 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
[12] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources

- *Prescribing Information Resources*[13]

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.[14]

- 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*.[15]

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.

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.

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[13] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources
[14] https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs
[15] 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.

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."

Reference ID: 5896202

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[16] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[17]. 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).

[16] https://www.fda.gov/media/84223/download
[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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, 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[18] 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.

[18] 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/

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