CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761094Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 115892 BLA 761094
Request Receipt Date	October 2, 2017
Product	OXERVATE; Recombinant Human Nerve Growth Factor (rhNGF)
Indication	Treatment of Neurotrophic Keratitis
Drug Class/Mechanism of Action	recombinant form of the human growth factor (rhNGF) produced in *E. coli*.; mechanism of action of the drug product is not known
Sponsor	Dompe farmaceutici s.P.a.
ODE/Division	OAP/DTOP
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	December 1, 2017

Note: This document should be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Treatment of (b) (4) Neurotrophic Keratitis (NK)

   The therapeutic indication pursued with OXERVATE is treatment of (b) (4) NK, (b) (4).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics"
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics"
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

- **A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

The proposed biologic product is OXERVATE eye drops solution which contains cenegermin, a recombinant form of the human growth factor (rhNGF) produced in *E. coli*. The mechanism of action of the drug product is not known. The population that the proposed drug product to treat are patients with (b) (4) neurotrophic keratitis.

Neurotrophic keratitis (NK) is a degenerative disease of the corneal epithelium resulting from impaired corneal innervation. The cause is damage to the trigeminal nerve (cranial nerve V) or its branches, causing corneal hypoesthesia or anesthesia. Impairment of the trigeminal innervation leaves the cornea susceptible to injury and decreases reflex tearing. Epithelial breakdown can lead to ulceration, infection, melting, and perforation secondary to poor healing. Management of NK is based on clinical severity, and the aim is to promote corneal healing and prevent progression of the disease to stromal melting and perforation.

There are currently no approved drug or biologic products to treat NK.

- **Information related to endpoints used in the available clinical data:**

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

For studies NGF0212 and NGF0214, the primary efficacy endpoint was "Greatest diameter of the corneal fluorescein staining in the area of the persistent epithelial defect (PED) or corneal ulcer being < 0.5mm."

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

The Division would accept the following primary efficacy endpoint:

- **Complete corneal clearing with no residual staining.**

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

- **A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

    - *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

    - *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are currently no approved drug or biologic product approved to treat this condition.

- **A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].**

There are no drugs or biologic products being studied for the same indication, or very similar indication, that requested breakthrough therapy designation.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Study (Phase)	Study Design	Treatment Group	Dose	Number of Subjects	Primary Endpoint
NGF0212 (Phase 2 Part of Phase1/2)	8 week, randomized, double-masked, vehicle-controlled, parallel group	Stage 2-3 NK	10 µg/ml 20 µg/ml Vehicle	52 52 52	"Complete healing" defined as "Greatest diameter of the corneal fluorescein staining in the area of the PED or corneal ulcer being < 0.5mm."
NGF0214 (Phase 2)	8 week, multicenter, randomized, double-masked, vehicle-controlled, parallel group	Stage 2-3 NK	20 µg/ml Vehicle	24 24	"Complete healing" defined as "Greatest diameter of the corneal fluorescein staining in the area of the PED or corneal ulcer being < 0.5mm."

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

No curative treatments exist for Stage 2 and 3 NK; unresponsive NK requires surgery, e.g. tarsorrhaphy, amniotic membrane transplantation and keratoplasty, etc.

The table below summarizes the results for complete corneal healing of the persistent epithelial defect or corneal ulcer (the primary endpoint, defined as absence of staining in the area of the lesion and non-persistent lesion in the rest of the cornea) after 8 weeks of treatment for patients who received OXERVATE or vehicle in the two studies. Analysis is post-hoc for NGF0212 because the Agency expects complete corneal healing, not partial healing, as originally proposed by the sponsor.

Table 3: Efficacy results (primary endpoint)

Results after 8 weeks of treatment		Study NGF0214	Study NGF0212
Complete corneal healing rate	OXERVATE	65.2	72.0 % *
	Vehicle	16.7	33.3 % *
	(p value)	(<0.001)	(<0.001)

* Results from a post-hoc analysis.

The most commonly reported adverse reactions in patients suffering from NK and treated with OXERVATE during clinical studies include eye pain (11%), eye inflammation (8%), which may include anterior chamber inflammation and hyphema; lacrimation increased (6%), with symptoms such as eye discharge; eyelid pain (6%) and foreign body sensation in the eye (6%).

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

There are currently no approved drug or biologic products to treat NK. No curative treatments exist for Stage 2 and 3 NK; unresponsive NK requires surgery, e.g. tarsorrhaphy, amniotic membrane transplantation and keratoplasty, etc. Tarsorrhaphy and aminiotic membrane transplantation does not permit useful visual function. Results from two Phase 2, randomized, double-masked clinical studies demonstrated highly statistically significant differences in complete healing between the test product and its vehicle.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
11/29/2017

WILEY A CHAMBERS
11/29/2017

RENATA ALBRECHT
11/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115892

MEETING MINUTES

Dompe farmaceutici S.p.A.
Attention: Robert J. McCormack, PhD.
Regulatory Affairs Consultant
14 Edinburgh Drive
Randolph, NJ 07869

Dear Dr. McCormack:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Recombinant Human Nerve Growth Factor (rhNGF).

We also refer to the meeting between representatives of your firm and the FDA on January 31, 2017. The purpose of the meeting was to discuss the plan submission of a BLA for recombinant human nerve growth factor (rhNGF), 20 μg/ml, for the treatment of neurotrophic keratitis.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Ms. June Germain, Safety Regulatory Project Manager at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	January 31, 2017 Time: 10:00 AM to 11:00 AM, EST
Meeting Location:	Location: 10903 New Hampshire Avenue White Oak Building 2, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 115892
Product Name:	Recombinant Human Nerve Growth Factor (rhNGF).
Indication:	treatment of neurotrophic keratitis
Sponsor/Applicant Name:	Dompe farmaceutici S.p.A.
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	June Germain, MS.

FDA ATTENDEES

Renata Albrecht, MD	Division Director
Wiley Chambers, MD	Deputy Director
Martin Nevitt, MD	Medical Reviewer
Rhea Lloyd, MD	Medical Reviewer
Abel Eshete, PhD	Statistical Reviewer
Yan Wang, PhD	Statistical Team Leader
Joshi Abhay, PhD	Clinical Pharmacology Reviewer
Seong Jang, PhD	Acting Clinical Pharmacology Team Leader
Aling Dong, PhD	Pharmacology/Toxicology Reviewer
Lakshmi Narasimhan, PhD	Product Quality Microbiology Reviewer
Monica Commerford, PhD	Product Quality Microbiology Reviewer
Frances Namuswe, PhD	Product Quality Reviewer
Maria Gutiettez-Lugo, PhD	Product Quality Team Leader
Derek Alberding	Regulatory Project Manager
June Germain, MS.	Safety Project Manager

SPONSOR ATTENDEES

Eugenio Aringhieri	CEO, Dompe
Lamberto Dionigi, MS	Regulatory Affairs, Dompe
Romeo Tiziana, MS	CMC Regulatory, Dompe
Flavio Mantelli, MD	Clinical Development, Dompe
Marcello Allegretti, MD	CSO, Dompe
(b) (4)	

1.0 BACKGROUND

Dompe is developing a topical ophthalmic solution of Recombinant Human Nerve Growth Factor (rhNGF) for the treatment of neurotrophic keratitis (NK) (b) (4)
On October 11, 2016, Dompe requested a pre-BLA meeting to discuss the plan submission of a BLA for recombinant human nerve growth factor (rhNGF), 20 µg/ml, eye drops solution in patients with (b) (4) neurotrophic keratitis. The meeting was granted for January 31, 2017.

On January 25, 2017, the FDA issued preliminary comments in response to the questions posted in the December 20, 2016 briefing document. On January 30, 2017, the sponsor emailed a handout for the meeting discussion on question 3 and further clarification regarding human PK data. The Sponsor also stated that all other FDA preliminary comments did not require clarification.

For the purposes of this response, the Sponsor questions are in **bold** font, FDA preliminary responses are in *italics* font, and the meeting discussion is in normal font.

2.0 DISCUSSION

<u>Question 1</u>. Does the FDA agree that the proposed delivery system which allows the use of the vial as multidose could be implemented for commercial distribution?

<u>FDA Response:</u> *We are providing you with the following recommendations to support the use of the proposed delivery mechanism:*

a. (b) (4)

b. The microbial challenge study discussed in the meeting package was performed using Stahylococcus aureus. A microbial challenge study with additional organisms including a spore former and the challenge organisms described in USP <51> should be performed to demonstrate the integrity of the vial adapter valve.

c. Sterilization validation data to support the sterility of the single-use, sterile disposable pipette and the disinfectant wipes should be submitted for review.

The adequacy of the proposed delivery system will be determined during BLA review. For additional quality considerations, please refer to the Agency advice letter dated November 17, 2016.

Meeting Discussion:
The Sponsor had no further comment.

Question 2. Does FDA concur that the clinical data collected in Phase II with (b) (4) could be considered representative of the delivery system specifically developed for rhNGF in the to be marketed, multi-dose vials??

FDA Response: *Potentially. The Agency will need to evaluate the full clinical study report from Study NGF0216 prior to making any determination about the adequacy of the efficacy and safety data to support the filing of a BLA. You are reminded that the Agency expects a BLA to be supported by at least two adequate and well-controlled trials, one of which uses the to be marketed formulation.*

Meeting Discussion:
The Sponsor had no further comment.

Question 3. Considering the high unmet medical need, and the fact that studies to build the safety database of 300 subjects exposed to rhNGF eye drops are on active recruitment, would FDA allow the submission of a BLA for this Fast-Track program by the time the last of the requested 300 subjects has started treatment?

FDA Response: *No. It is expected that the application be complete at the time of the filing of the BLA. All the data that you intend to use to support the BLA should be included in the application. This includes a safety database of at least 300 subjects exposed at or above the proposed dose at the time of the BLA filing.*

Meeting Discussion:

- The Sponsor stated that they are collecting additional safety data from ongoing studies (NGF0116, NGF0216, NGF0314) using the methionine formulation. The Sponsor noted that the results of these remaining studies are expected to confirm the already completed studies.
- The Sponsor stated that the BLA is planned to be submitted no sooner than the last patient enrollment in the additional safety studies. And that the BLA submission will be planned in order to have the additional safety data submitted no later than 3 months after the BLA submission.
- The Division stated that based on user fee policy, all applications must be complete at the time of the BLA filing. The Division noted that this policy ensures that studies are completed and that the development phase does not run into the Agency's review time period.
- The Division stated that if the product has been granted fast track designation then the Agency would accept for submission a complete section of a BLA, such as the CMC

section and/or the nonclinical section. The Division noted that these sections must be complete and not in draft form. The Division also stated that all manufacturing facilities should be ready for inspection at the time the CMC section is submitted.

- The Sponsor stated that they are awaiting the final comments from the EMA and will then combine the data and submit the CMC and nonclinical section after the April 2017.

Question 4. Does FDA agree with the Common Technical Document (CTD) table of content proposed for the submission of a BLA? More specifically:

a) With the location of the reports for the clinical studies;

FDA Response: *Agree. We note that you plan to submit reports for Study NGF0112 (Phase 1 in healthy volunteers) and PK data from NK patients in Module 5.3. We recommend that you also submit a aggregated summary of Clinical Pharmacology findings (PK and immunogenicity) from all the applicable studies in Module 2.7.2.*

b) With the location of information relevant to the delivery system.

FDA Response: *Agree. It appears that Module 5 does not contain "datasets" and the subfolders for "tabulations" and "analysis" for each study. Please submit the following for each study:*

(1) The raw datasets with a defined document in the "tabulations" folder and the analysis datasets with a defined document in the "analysis" folder and
(2) All programming codes used to derive the analysis datasets and to generate the efficacy and safety results.

Please clarify the content of the process validation report annex under Module 3.2.R.1, Process Validation of the Drug Product. Information and studies related to the process validation of the Drug Product should be provided in Module 3.2.P.3.5, Process Validation and/or Evaluation.

For additional comments on the CTD table of contents, please refer to the Additional Comments section at the end of this document.

Meeting Discussion:
The Sponsor had no further comments.

Question 5. Does FDA have any comments on the draft Product Information proposed for the product?

FDA Response: *No, not at this time. Labeling discussions are deferred until review of the BLA has been completed.*

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) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30,

2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- *The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.*
- *The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.*
- *Regulations and related guidance documents.*
- *A sample tool illustrating the format for Highlights and Contents, and*
- *The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.*
- *FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.*

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Meeting Discussion:
The Sponsor had no further comments.

Question 6. Does FDA agree that a PREA can be waived given the Orphan Drug Designation for rhNGF for the treatment of NK?

FDA Response: *We agree that PREA is not applicable for this drug product for the treatment of neurotrophic keratitis.*

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 an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of

your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

Additional Agency Comments:
We are providing additional product quality microbiology comments for you to consider for the preparation of your BLA 351(a) submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
- *Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5). Hold time studies may not be required if closed single-use gamma-irradiated systems with in-line filter are used.*
- *Provide chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples to demonstrate adequate microbial control at scale. In addition, provide the bioburden and endotoxin acceptance criteria for resin and membrane storage. Bioburden and endotoxin samples for the storage validation study should be taken at the end of storage prior to sanitization (3.2.S.2.5).*
- *Bioburden and endotoxin data obtained during manufacture of at least three PPQ lots (3.2.S.2.5).*
- *Information and summary results from the shipping validation studies (3.2.S.2.5).*
- *Drug substance bioburden release specifications (3.2.S.4).*
- *Summary report and results from bioburden and endotoxin test method qualification performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).*

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the aseptic process and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry,

Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" at
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- *Identification of the manufacturing areas and fill line, including area classifications.*
- *Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.).*
- *Sterilizing filtration parameters.*
- *The wetting agent used for post-use integrity testing of the sterilizing filter and the acceptance criterion for passing post-use integrity testing.*
- *Parameters for filling, stoppering, and capping.*
- *Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.*
- *Processing/hold time limits, including the time limit for filtration.*
- *Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.*

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- *Bacterial filter retention study for the sterilizing filter.*
- *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program. For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.*
- *In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.*
- *Isolator decontamination, if applicable.*
- *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.*
- *Capping validation demonstrating maintenance of container closure integrity.*
- *Information and summary results from shipping validation studies.*

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- *Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry.*
- *Summary report and results for qualification of the bioburden, sterility and in process endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.*

Meeting Discussion
Sponsor request for clarification on human PK

2016 Type C meeting FDA Comment: *As part of your clinical development program, we recommend that you attempt to determine systemic PK exposures to rhNGF following repeated topical ocular dosing of the proposed to-be-marketed rhNGF ophthalmic solution containing methionine. This can be performed in a subset of approximately 8 to 10 NK patients as part of a clinical trial, or as a separate PK, safety, tolerability study in approximately 8 to 10 healthy volunteers.*

Sponsor January 30, 2017 response:

- Absence of any increase above baseline of endogenous NGF levels following repeated topical ocular dosing of formulation without methionine
- No systemic immunogenicity detected in any of the clinical studies, including those with methionine formulation

Sponsor January 30, 2017 question:
Based on the absence of systemic exposure and immunogenicity, could FDA accept a post-approval commitment to provide specific PK data on the methionine containing formulation?

Meeting Discussion

- The Division noted that the provided rationale for a post-approval PK assessment with the methionine containing formulation appears reasonable. However, the Division requested that the Sponsor provide the PK data from rabbit studies that simultaneously compared two formulations of rhNGF, i.e., the formulations with methionine and without methionine, before the BLA is submitted. The Division clarified that the final determination on acceptability of the proposed post-approval commitment will be made based on the collective information from Study NGF0112, Study NGF0212, and the applicable rabbit PK studies.

3.0 ACTION ITEMS

- The Sponsor agreed to submit the completed rabbit PK studies and a summary of the PK results from Study NGF0112 and Study NGF0212 to the IND for review before the BLA is submitted.

4.0 ATTACHMENTS AND HANDOUTS

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/s/

WILEY A CHAMBERS
02/10/2017