CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761134Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 112198

MEETING MINUTES

Generon (Shanghai) Corporation
c/o Everest Clinical Research
Attention: Roberta Smithey
Regulatory Affairs Consultant
150 Clove Road, Suite 502
Little Falls, NJ 07424

Dear Ms. Smithey:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for F-627.

We also refer to the teleconference between representatives of your firm and the FDA on May 1, 2020. The purpose of the meeting was to discuss aspects of the clinical, CMC, and nonclinical sections of the F-627 BLA 761134.

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

If you have any questions, call Esther Park, Senior Regulatory Health Project Manager, at (301) 796-2811.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Non-Malignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[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.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: Friday, May 1, 2020; 9:00 – 10:00 AM (ET)
Meeting Location: Teleconference

Application Number: IND 112198
Product Name: F-627
Indication: To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Sponsor Name: Generon (Shanghai) Corporation

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Esther Park, PharmD

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Ellis Unger, MD, Director

OCHEN/Division of Non-Malignant Hematology
Ann T. Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases
Esther Park, PharmD, Senior Regulatory Health Project Manager

OCHEN/Division of Pharmacology/Toxicology
Todd Bourcier, PhD, Director

Office of Biostatistics/Division of Biometrics IX
Yeh-Fong Chen, PhD, Statistics Team Leader
Lola Luo, PhD, Statistics Reviewer

Office of Biotechnology Products/Division of Biotechnology Review & Research IV
Chana Fuchs, PhD, Product Quality Team Leader
Jee Chung, PhD, Product Quality Reviewer

Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing
Thuy Thanh Nguyen, PhD, Branch Chief
Candace Gomez-Broughton, PhD, Quality Assessment Lead
Maxwell Van Tassell, PhD, Product Quality Microbiology and Facility Reviewer

SPONSOR ATTENDEES

Generon Corporation
William L. Daley, MD, MPH, Chief Medical Officer, Generon Corporation, USA
Hanyang Chen, PhD, Director, CMC Analytical Development, Generon Corporation, Shanghai
Zhihua Huang, MA, Director, Pre-clinical CMC Development, Generon Corporation, Shanghai
Catrina Wang, MD, Medical Lead, China
John Zang, PhD, Medical Manager, China
Chong Xiao, MA, Director, Regulatory Affairs, Generon Corporation, Shanghai
Yonghong Cheng, MA, Associate Director, Regulatory Affairs, Generon Corporation, Shanghai

Consultants
(b) (4) CMC Consultant
(b) (4) Principle Statistician
(b) (4) Product Development Consultant
Roberta Smithey, BSc, Authorized Representative for Generon Regulatory Affairs

Everest Clinical Research Corporation
(b) (4)

1.0 BACKGROUND

F-627 is a 413-amino acid recombinant fusion protein that contains human granulocyte colony stimulating factor (G-CSF) and a human IgG2-Fc fragment, with a 16-amino acid peptide linker. The Sponsor, Generon (Shanghai) Corporation, is currently developing

F-627 to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

On March 2, 2020, the Sponsor requested a Type B meeting to discuss aspects of the clinical, CMC, and nonclinical sections of the F-627 BLA 761134. Generon (Shanghai) Corporation is completing the final Phase 3 trials for F-627 and is planning to submit the BLA in the fourth quarter of 2020.

FDA sent Preliminary Comments to Generon (Shanghai) Corporation on April 23, 2020.

2.0 DISCUSSION

2.1. Clinical Efficacy

ISE Analysis Populations

Question 1: *Does the Agency agree with the proposed ISE strategy with respect to the studies chosen, analysis populations, and efficacy endpoints?*

FDA Response to Question 1:
In general, the proposed ISE strategy appears acceptable. However, we would like to emphasize that the labeling claim(s) of F-627 will be based on the results of the individual phase 3 pivotal studies. The results from the ISE analysis will be exploratory and can be used to provide supportive evidence.

The proposed ISE strategy with respect to the studies chosen, analysis populations, and efficacy endpoints seems reasonable. However, we note that you are not planning to conduct subgroup efficacy analyses other than by age. Please provide the percentages of patients who are non-White (i.e., Black/African American, Asian, other) in the pivotal trials. Preferentially, the following minimum subgroup analyses should be conducted for the primary endpoint for the pivotal trials: age, race, and weight.

In the SAP for the ISE, you stated that the treatment differences for the various efficacy endpoint analyses will be estimated as mean (F-627 20 mg) minus mean (comparator), with 2-sided 95% Wald CIs; the normality of the data will be inspected visually. In addition to your proposed method, we recommend use of an ANCOVA model to compare the treatment difference for continuous endpoints such as the duration of severe neutropenia (DSN), while adjusting for important covariates. The normality assumption should be assessed based on a proper statistical test rather than visual inspection. For the discrete endpoints, the treatment difference can be estimated using a (stratified) Cochran-Mantel-Haenszel (CMH) test. You state that

p-values will not be calculated because they would be retrospective. We agree, given that no inferential conclusions will be made from these analyses.

Discussion: **The Sponsor explained that analyses by racial sub-groups is not feasible because there are too few non-white subjects (i.e., one) enrolled in the randomized subject population. Regarding analysis by weight subgroups, the Sponsor had proposed analyses based on weight <65 or ≥65 kg. The Agency recommended that additional weight categories (i.e., more than two subgroups), such as quartiles, be used. The Sponsor noted that there are important differences in weight across the studies (in particular, one study in Japan with patients of lower body weight) that would skew a 4-category analysis. The Sponsor suggested analyses based on 3 weight categories rather than 4, and the Agency agreed that this would be sufficient. The Sponsor will consider the Agency's recommendation.**

The Sponsor questioned whether the above subgroup analyses should be carried over into the safety analysis (ISS). The Agency responded that the Sponsor should also conduct subgroup analysis on weight for ISS.

The Agency explained that labeling claims would be based on the results of the individual phase 3 pivotal studies, and not integrated analyses from the ISE, though the latter could be used as supportive evidence. The Sponsor expressed understanding on this point.

The Sponsor agreed to add covariate-adjusted analyses (specifically to generate confidence intervals), as identified in the proposal, i.e., ANCOVA for continuous endpoints and CMH for discrete endpoints. The Agency acknowledged that some flexibility may be needed in applying strata on various discrete endpoints because of sparse cell counts and suggested that pooling of strata may be useful. Furthermore, the Agency agreed that hypothesis testing for statistical comparisons will not be needed for the subgroup evaluations as they are exploratory in nature; providing the confidence intervals for the subgroup analyses will be acceptable.

Missing Data Imputation Strategy

Question 2: *Does the Agency agree with the missing data imputation strategy for the primary endpoint in each study included in the ISE analyses?*

FDA Response to Question 2:
The proposed strategy for imputation of missing data appears acceptable. We recommend the use of the ANCOVA model to test each imputed duration of Grade 4 (severe) neutropenia while adjusting for important covariates, instead of the proposed t-test in step 4 of the sequential regression imputation under Rule C (Fully Conditional Specifications Method).

We recommend that you conduct additional sensitivity analyses that include imputation methods based on the missing not at random (MNAR) assumption (e.g., tipping point analysis and jump to reference analysis) to further assess the impact of missing data on the primary endpoint. For further advice on missing data, see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials. An electronic version of the document can be found from The National Academies Press at http://www.nap.edu/catalog.php?record_id=12955. A special report of the document can be found at http://www.nejm.org/doi/full/10.1056/NEJMsr1203730.

Discussion: **The Agency acknowledges that the Sponsor's proposal seems acceptable.**

2.2. Clinical Safety

Adverse Event Analysis Plan for the ISS

Question 3: *Does the Agency agree with the study populations and adverse event analysis plan for the ISS?*

FDA Response to Question 3:
The proposed study populations and AE analysis plan for the ISS appear reasonable.

Discussion: **No discussion occurred.**

Adverse Events of Special Interest

Question 4: *Does the Agency agree with the planned AESIs for inclusion in the ISS?*

FDA Response to Question 4:
No, the Agency does not agree. We have the following comments:

- In addition to the proposed AESIs, the list should also include the potential for tumor growth stimulatory effects on malignant cells and injection site reactions.

- In addition to the plan for presentation of serious allergic reactions you propose, defined as subjects who have adverse events with preferred terms from at least two of the three groups, please include a presentation of allergic reactions incorporating a finding of seriousness based on outcomes of death, life-threatening adverse event, inpatient hospitalization or prolongation of

existing hospitalization, or persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Also, in addition, to the selected PTs you include (under the anaphylactic reaction SMQ) in the assessment for serious allergic reactions, please include Preferred Terms under the hypersensitivity SMQ (narrow) and all other PTs under the anaphylactic reaction SMQ (narrow).

- In your submission, provide the narratives of patients who experience splenic rupture, acute respiratory distress syndrome, serious allergic reactions, sickle cell crises in patients with sickle cell disorders, glomerulonephritis, capillary leak syndrome or aortitis.

Discussion: **The Sponsor agreed with the updated AESI to be included in the analysis and provided a table summarizing selection of terms. (See Table 1 under "Generon Response to FDA Comments on Question 4" in the Sponsor's response document attached below). The Agency agrees with the Sponsor's proposal at this time. However, the Agency indicated that we will also be conducting FDA MedDRA queries (in addition to standard MedDRA queries) that may identify new safety issues and generate requests for additional analyses during the review. The Sponsor agreed to perform additional analyses as a result of the queries at the Agency's request.**

The Sponsor agreed to provide patient narratives as requested in the FDA response.

F-627 Treatment Grouping

Question 5: *Does the Agency agree with the proposed F-627 treatment grouping for the ISS analyses?*

FDA Response to Question 5:
The proposed F-627 treatment grouping for the ISS analyses is acceptable. However, you state that pre-filled syringe (PFS) liquid formulation was used in the three phase 3 studies (GC-627-04, GC-627-05, SP11631) and that for ISS analysis subjects receiving F-627 20 mg (lyophilized formulation or PFS) as a fixed dose will be assigned to the "F-627 20 mg" arm. In the datasets, you should include flags for "lyophilized formulation" and "PFS." In your BLA submission, provide safety comparisons between the two formulations.

Discussion: **No discussion occurred.**

Placebo Treatment Arm

Question 6: *Does the Agency agree with the analysis plan for handling the placebo data in the ISS and ISE?*

FDA Response to Question 6:
We agree with your proposed analysis plan for handling the placebo data in the ISS. For the ISE, we agree that the efficacy results of the placebo arm should be reported separately. With regard to labeling, as the primary endpoint in study GC-627-04 is the duration of grade 4 neutropenia observed in chemotherapy Cycle 1, it is unlikely that efficacy results from Cycles 2-4 will be included.

Discussion: **No discussion occurred.**

Study SP11502 Classified in Other Studies Section

Question 7: *Does the Agency agree with the classifying of study SP11502 in the "Other Studies" section for the ISS and ISE?*

FDA Response to Question 7:
Yes.

Discussion: **No discussion occurred.**

2.3. Study Data Standardization Plan

Study Dataset Format

Question 8: *Does the Agency agree with the plan for clinical and nonclinical dataset submission, as detailed in the SDSP?*

FDA Response to Question 8:
The proposed plan for clinical and nonclinical dataset submission is acceptable.

In addition, we have a few comments for the clinical data submission:

- FDA requests that an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission, be prepared and submitted in the BLA. Please refer to the "Study Data Technical Conformance Guide: Technical Specifications Document," available at: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf.

- Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s) to ensure efficient review.

- Provide executable SAS program(s) with adequate document(s) to allow FDA to duplicate the analysis datasets derivation from raw datasets.

Discussion: **No discussion occurred.**

2.4. Chemistry, Manufacturing and Control

Master Cell Bank (MCB) (b) (4)

Question 9: *Does the Agency agree that* (b) (4) *provide sufficient assurance* (b) (4) *of the F-627 MCB?*

FDA Response to Question 9:
Based on the information provided, and the lack of certain information identified below, we cannot agree at this time that the data available provide sufficient assurance (b) (4) of the F-627 MCB. Therefore, in the BLA submission, provide additional information for the following:

(b) (4)

If sufficient assurance (b) (4) is not provided, the control strategy necessary to support licensure and the data required to support manufacturing

changes post licensure should be sufficiently robust to ensure that the product quality is maintained throughout its lifecycle.

Discussion: **The Sponsor provided pre-meeting responses that included a description** [redacted] **The Agency requested that the study reports and any additional data needed to support the capabilities and sensitivities of the assays used be provided in the BLA. During BLA review, an assessment of these data** [redacted] **will be reviewed as part of the assessment of the appropriateness of the proposed control strategy.**

Stability Data to Support the Proposed F-627 Drug Product Shelf Life

Question 10: *Does the Agency agree with the approach to provide DP stability data to support a proposed 36 months shelf life for F-627 at BLA filing?*

FDA Response to Question 10:
In general, the approach to provide the stability data proposed in Table 9 of the meeting package that includes a simple stability data update within 30 days after BLA submission can be acceptable. However, the decision to grant the request for 36-month shelf-life for the DP will depend on the review of all DS and DP stability and characterization data provided in the BLA, as well as details on the manufacturing processes for each of the DS and DP processes by which the specific lots were manufactured. For any changes made to DS or DP manufacturing, including scale, manufacturing line, holding vessels, etc. detailed information comparing the processes and assessing risk to stability based on those processes should be included in the BLA submission.

Discussion: **No discussion occurred.**

FDS Shipping Validation

Question 11: *Considering F-627 FDS is shipped* [redacted] *does the Agency agree that the FDS shipping validation approach is acceptable to support the F-627 BLA filing?*

FDA Response to Question 11:
The proposal appears acceptable based on the general description of the performance qualification runs that includes minimum and maximum loads, maximum duration, and different seasonal times with [redacted] DS and the intent to

measure temperature and DS container integrity. Be sure to include details such as shipping and packing configurations, as well as (b) (4) locations etc., in the BLA. Any proposed allowances for excursions (b) (4) would require that shipping validation include a product quality assessment as part of that study.

Discussion: **No discussion occurred.**

2.5. Nonclinical

Totality of Nonclinical Data

Question 12: *Does the Agency agree that the F-627 nonclinical program is complete and sufficient to allow for BLA filing and review?*

FDA Response to Question 12:
We agree that the nonclinical program appears sufficient in scope to support the BLA submission and review of F-627. The adequacy of the data will be assessed during the review of the BLA.

Discussion: **No discussion occurred.**

2.6. Regulatory

Questions Related to "the Program" Under PDUFA VI

Question 13: *Does the Agency agree that the proposed BLA contents outlined in Appendix 1 represent a complete application?*

FDA Response to Question 13:
No.

The clinical and nonclinical studies appear adequate for the proposed BLA submission. However, the final determination on filing will be made after submission of the application and determination of adequacy to support approval will made during the review of the BLA.

Please also refer to the Microbiology comments below regarding contents that address facilities and information for inspections.

The Agency does not agree with the format for the following modules:

Regarding Modules 1.1.1 and 1.1.2, please note that additional nodes should not be created beyond what is in the eCTD structure specifications. Please follow https://www.fda.gov/media/76444/download for more details regarding the eCTD

structure specifications. Instead, leaf titles can be used to differentiate between documents in Module 1.1.

Regarding Modules 2.3.1, please note that the "Introduction" should be submitted under 2.3. Module 2.3.1 is not an acceptable node.

Similarly, for Module 3.2.P.2, Modules 3.2.P.2.1.1, 3.2.P.2.1.2, 3.2.P.2.2.1, 3.2.P.2.2.2, and 3.2.P.2.2.3, are not acceptable nodes. However, these sections can be included within the documents under the 3.2.P.2.1 and 3.2.P.2.2 levels or multiple documents may be submitted at the 3.2.P.2.1 and 3.2.P.2.2 levels with each document having a specific title to easily identify the topic/contents of the document.

Further, any nodes created under Modules 4.2.1.1, 4.2.1.3, 4.2.2.1, 4.2.2.2, 4.2.2.3, 4.2.2.7, 4.2.3.2, 4.2.3.5.1, 4.2.3.5.2, 4.2.3.5.3, 4.2.3.6, 4.2.3.7.1, 5.3.1.4, 5.3.3.1, 5.3.3.2, 5.3.3.5, 5.3.4.1, 5.3.4.2, 5.3.5.1, and 5.3.5.3 are not acceptable. However, multiple documents may be submitted at the levels provided above. Typically, a single document should be provided for each study report. Leaf titles can be used to differentiate between documents submitted under each Module. For further guidance on acceptable submission format per Module, please follow https://www.fda.gov/media/71551/download.

From a technical perspective (and not content related), the organization of the other modules is acceptable.

Discussion: **No discussion occurred.**

Question 14: *Does the Agency agree that updated DP stability data may be submitted within 60 days of the original application?*

FDA Response to Question 14:
No. However, we can agree to a stability data update within 30 days of the original BLA submission.

Discussion: **No discussion occurred.**

Question 15: *Does the Agency agree that a REMS may not be necessary for F-627 if the observed safety profile is similar to that for pegfilgrastim?*

FDA Response to Question 15:
The Agency agrees that if the observed safety profile of F-627 is similar to that of pegfilgrastim, a formal REMS may not be necessary for F-627. However, the final determination will made during the review of the BLA.

Discussion: **No discussion occurred.**

ADDITIONAL COMMENTS

Chemistry, Manufacturing and Controls

1. A [redacted] (b) (4) drug substance manufacturing process (IND amendment #60/eCTD #0029 on 1/10/2019). The BLA should include updated [redacted] (b) (4) study data [redacted] (b) (4) [redacted] (b) (4)

2. To facilitate the Agency's review of the manufacturing processes for the DS and DP, provide 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 provided below. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this Table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Title: INSERT UNIT OPERATION

Process parameter/ operating parameter/In-process control (IPC)/In-process tests (IPT)[1]	Proposed Range for Commercial Manufacturing[2]	Criticality classification[3]	Characterized Range from process development[2]	Manufactured Range from process validation[2]	Justification of the proposed commercial acceptable range[4] (or link to eCTD)	Comment[5]

[1]Terminology should be adapted to the one used by Generon.
[2]As applicable.
[3]For example, critical process parameter, non-critical process parameter, as described in Module 3.
[4]This could be a brief verbal description (e.g, "development range", "validation range", or "platform experience") or links to the appropriate section of the eCTD.
[5]Optional.

3. To facilitate the Agency's review of the control strategy for F627, provide information for critical quality attributes and process and product related impurities for the DS and DP in the following tabular format. The tables should summarize information from Module 3 and may be submitted either to module 1 or Module 3R. Note, this Table does not replace other parts Module 3 or impact the nature or amount of information included in those parts of Module 3.

Title: INSERT DRUG SUBSTANCE, OR DRUG PRODUCT

Critical Quality Attributes (including Process and Product related impurities for DS and DP)	Impact[1]	Source[2]	Analytical method[3]	Proposed control strategy[4]	Justification of the proposed control strategy[5]	Comment[6]

[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 the methods used as part of the control strategy 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, e.g., in-process testing, validated removal, release testing, stability testing.
[5]This could be a brief verbal description or links to the appropriate section of the eCTD
[6]Optional.

Discussion: **No discussion occurred.**

Microbiology

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The 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. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).

- Microbial data from three successful 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).

- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).

- Information and summary results from the shipping validation studies (3.2.S.2.5).

- Drug substance bioburden and endotoxin release specifications (3.2.S.4).

- Summary reports and results from bioburden and endotoxin test method qualification studies 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 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. 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 type of fill line (e.g. open, RABS, isolator), including area classifications.

- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.

- Parameters for filling and plunger placement for the pre-filled syringes.

- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.

- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.

- 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, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.

- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.

- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, 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.

- Information and summary results from shipping validation studies. For prefilled syringes, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled

syringe plunger movement during air transportation does not impact product sterility.

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 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 every 12 months (annually) until expiry.

- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished 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. Provide full descriptions and validation of non-compendial rapid microbial methods.

- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).

- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.

Additionally, we note that current specifications for endotoxins are expressed by weight (EU/mg). Endotoxin in the process is a consequence of microbial ingress and is independent of product concentration. Therefore, endotoxin limits should be reflected volumetrically for liquid DS and DP in-process controls and release specifications to be consistent batch-to-batch per process capability.

Discussion: **The Sponsor agreed to provide all requested information in the relevant BLA sections. The Sponsor agreed that endotoxin limits will be reported as EU/mL.**

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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) 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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

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*.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

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, NDA/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)				

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*.[6]

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.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

[6] https://www.fda.gov/media/85061/download

5.0 ACTION ITEMS

There were no action items identified.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response document to the Agency's meeting preliminary comments is appended to these minutes.

24 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

KATHY M ROBIE SUH
05/06/2020 08:06:27 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112198

MEETING MINUTES

Generon (Shanghai) Corporation
Attention: Robert G. Ferraino
Regulatory Consultant
404 Saw Mill Road
East Berne, NY 12059

Dear Mr. Ferraino:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for F-627.

We also refer to the teleconference between representatives of your firm and the FDA on December 1, 2015. The purpose of the meeting was to discuss the clinical and non-clinical Phase III development program.

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

If you have any questions, call Tinya Sensie, Regulatory Project Manager at (240) 402-4230.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology 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:	End of Phase 2
Meeting Date and Time:	December 1, 2015**;** 3:00 PM- 4:00 PM (ET)
Meeting Location:	Teleconference
Application Number:	IND 112198
Product Name:	F-627
Proposed Indication:	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer therapy associated with a clinically significant incidence of febrile neutropenia.
Sponsor/Applicant Name:	Generon (Shanghai) Corporation
Meeting Chair:	Albert Deisseroth, MD, PhD, Clinical Team Leader
Meeting Recorder:	Tinya Sensie, MHA, Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP)

Ann Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Albert Deisseroth, MD, PhD, Clinical Team Leader
Patricia Dinndorf, MD, Clinical Reviewer
Tinya Sensie, MHA, Regulatory Project Manager

Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology (DCPV)

Bahru Habtemariam, PharmD, Acting Clinical Pharmacology Team Leader
Xianhua Cao, Clinical Pharmacology Reviewer

Office of Biostatistics (OB)/Division of Biometrics V (DBV)

Yuan Li Shen, PhD, Biostatistics Team Leader
Yaping Wang, PhD, Biostatistics Reviewer

Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research (DBRR)

Jee Chung, PhD, Team Leader
Brian Janelsins, PhD, Reviewer

SPONSOR ATTENDEES

Tom Tang, MD, Chief Medical Officer and head of Regulatory Affairs, Generon (Shanghai) Corporation
Yan Xiaoqiang, PhD, Chief Scientific Officer, Generon (Shanghai) Corporation
(b) (4) Clinical Oncologist, (b) (4)
(b) (4) Regulatory Consultant
(b) (4) Clinical Operations Consultant
(b) (4) Biostatistician Consultant, (b) (4)
(b) (4)
(b) (4)

1.0 BACKGROUND

On July 10, 2015, Generon (Shanghai) Corporation submitted an End-of-Phase 2 meeting request for IND 112198 for F-627 to discuss the clinical and non-clinical Phase III development program. DHP granted them a type B meeting.

F-627 is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer therapy associated with a clinically significant incidence of febrile neutropenia.

The meeting was cancelled due to inclement weather. After reviewing FDA's preliminary responses Generon requests the following questions 3, 5, 8, 10 and an additional question be discussed at the rescheduled meeting. The preliminary responses for the previously scheduled meeting were issued October 1, 2015 and the full document is appended to these meeting minutes.

FDA sent Preliminary Comments to Generon (Shanghai) Corporation on November 24, 2015.

2. DISCUSSION

Preamble

The meeting package you submitted to the FDA on October 30, 2015 for an End of Phase 2 Type B "CMC Only" Meeting indicates that the following changes will be made to the F-627 product:

- The formulation and presentation of F-627 will be changed from a lyophilized product to a solution concentrate with accompanying changes (b) (4) (b) (4)
- There also will be a change of manufacturing sites for F-627 drug substance and drug product.
- There will also be a change in some of the manufacturing procedures used for F-627.

The preliminary response to the questions for the meeting originally scheduled for October 5, 2015 and now scheduled for December 1, 2015 was based on the assumption that the development plan in question referred to the original formulation and drug substance and drug product of F-627.

Because Generon has made the decision to make these major changes, Generon should carry out a comparability exercise to bridge between the old manufacturing sites and procedures and the new. In addition to carrying out these comparability exercises, Generon should also conduct a PK/PD study in human subjects to assess the changes that may occur as a result of the proposed changes in formulation and manufacturing of F-627.

We also note that all of your phase 2 doses (80, 240 and 320 mg/kg) have similar efficacy profiles and that you have not identified the lowest dose consistent with maximal granulocyte colony-stimulating activity. Your PK-PD model is built based on limited data and provides limited utility in identifying the optimal dose.

Generon should therefore carry out the following studies to provide justification of the dose of F-627 proposed for the phase 3 trial.

- Conduct integrated dose-response analysis using available pharmacodynamics, safety and efficacy data in order to identify a dose that provides preliminary evidence of acceptable safety and efficacy profile.
- If you do not have sufficient dose levels to conduct the recommended analyses described in the previous bullet, you may wish to evaluate additional dose levels.

As a result of the aforementioned issues, all advice given in the FDA responses below and all discussion in the face to face meeting on December 1, 2015 refers to the original formulation of F-627 which was manufactured by the original procedures and at the original sites.

The Agency does not have enough information to provide answers for the new formulation which is proposed to be manufactured with new modifications and at different sites.

Discussion: *No discussion occurred.*

Question 3: **We propose to continue to perform immunogenicity testing using methods described below in each of our Phase III pivotal studies.**

Does the Agency concur?

FDA 10/1/15 Response to Question 3:

FDA agrees that continued immunogenicity testing of F-627 is needed for clinical development. Regarding the test methods, detailed descriptions of the immunogenicity assays and the validation reports for the screening (binding), confirmatory, and neutralizing activity assays were not provided in the meeting package; therefore, the FDA cannot determine the appropriateness of these assays for the testing of clinical samples in the proposed Phase III pivotal studies. Submit the validation study report data for the immunogenicity assays prior to testing clinical samples from the Phase III pivotal studies.

Updated Generon Meeting Materials Submitted 10/31/15

As requested by the Agency, the sponsor provided two assay validation reports for testing immunogenicity in patient serum samples after F-627 dosing. The validation parameters and results for the binding assay are summarized in Table 3. The validation parameters and results for the cell-based neutralizing assay are summarized in Table 4. The validation reports "for detection of anti-F-627 antibody in human serum using binding and confirmatory assay (BioA-V-001)" and "for detection of anti-F-627 antibody in human serum using cell based neutralizing assay (BioA-V-002)" are provided in Appendices 1 and 2. A comparison of Phase II assay validation parameters and the planned phase III validation is provided in Table 5 (for binding assay) and Table 6 (for neutralizing assay).

Updated Question 3: Can the agency comment on the appropriateness of these assays for the testing of clinical samples in the proposed Phase III pivotal studies?

FDA Response

While the FDA agrees with the overall validation approach for the immunogenicity assays described in the meeting package, a more detailed response regarding the adequacy of the assays cannot be provided at this time based on the limited information submitted. Until the assays are validated for testing of Phase 3 pivotal material, patient serum samples should be banked. The FDA has the following clarifications and general recommendations to be incorporated in the validation of the assays to be used for the Phase 3 studies:

1. The sponsor plans to use 30 normal human serum samples and 30 pre-dose (F-627) patient serum samples to determine the cut-points for both the binding and neutralizing assays. It is recommended that the number of serum samples used for cut-point determination range from 50 to 100 individual patient subjects.

2. Floating cut-points with run-specific correction factors were calculated for testing of Phase 2 material based on the assumption of normally distributed data. However, supporting data and statistical analysis were not provided to determine the suitability of the determined assay cut-points. Data and statistical analysis should be provided to support the assay validation cut-points that will be used to test Phase 3 material.

3. Samples with pre-existing antibodies and samples that are statistically determined to be outliers (unusually low or high signals) should be excluded from statistical evaluation of the assay cut point.

4. The neutralization assay measures the inhibition of proliferation of NFS-60 cells in response to the F-627. However, the submitted information for the neutralization assay did not specify the product concentration that will be used during the validation study and a concentration-response curve to indicate the suitability of the chosen product concentration. A concentration-response curve should be included in the validation studies and the product concentration to be used should lie on the linear range of the curve.

5. Assay specificity for the binding and neutralization assays utilizes a comparison of spiked and unspiked samples. The comparison of spiked and unspiked responses does not address assay specificity, which is typically assessed by spiking of irrelevant antigen, or for the neutralization assay, a second stimulus that exhibits similar cellular response as the product.

6. Refer to "Additional CMC Comment #2" in FDA responses to CMC-only pre-IND meeting questions (sent 06/29/2011) for previously submitted FDA recommendations on assay development and validation. In addition to the referenced guidance documents, we refer you to the following additional guidance documents:

    - USP-NF. General Information, <1106> Immunogenicity assays – design and validation of immunoassays to detect anti-drug antibodies.

    - USP-NF. General Information, <1106.1> Immunogenicity assays – design and validation of assays to detect anti-drug neutralizing antibodies.

Discussion: *No discussion occurred.*

Question 5: **The sponsor considers a fixed dose of (b) (4) 20 mg in a single dose prefilled syringe to be an appropriate dose for the proposed Phase III clinical program. The fixed dose justification is based on clinical trial experience, PK/PD results and PK/PD modeling.**

Does the Agency concur?

FDA 10/1/15 Response to Question 5:

No. You have not sufficiently justified your proposed phase 3 doses for the following reasons:

- Your PK/PD model was based on very limited dataset, with data obtained from 3 dose levels. The phase one data show maximum Pharmacodynamic effect at a dose of 240 µg/kg.
- The phase 2 data also indicate the three dose levels have similar clinical response rates.
- Your phase 1 and phase 2 trials were conducted using weight based dosing regimen. You have not provided any justification showing flat dosing will provide consistent exposure across different weight ranges.

We recommend you pool all available PK, PD, safety, and efficacy data and conduct an integrated dose-response analysis to justify your phase 3 doses. We also recommend you evaluate two distinct dose levels in your planned phase 3 trials.

Updated Generon Meeting Materials Submitted 10/31/15

Rationale for fixed doses for the proposed phase III studies is summarized in Table 7. The proposed fix dose of (b) (4) 20 mg of F-627 are within the dose range used in previous clinical studies. No significant safety issues were identified during the five clinical studies conducted previously. The supporting information including PK and PD results in clinical studies is presented below. In preclinical studies, F-627 has demonstrated a similar PK and PD profile to that of pegfilgrastim. Clinical studies that evaluated the PK and PD profile of F-627 are listed in Table 8.

Updated Question 5: Does the Agency concur with the current analysis proposal? Does this plan address the agency's previous recommendation?

FDA Response

No. As you are making major changes to the manufacturing and formulation of the product, you will need to conduct PK and PD studies in healthy subjects with the new formulation before initiating further development (see preamble above).

In addition see the comments in the preamble regarding appropriate approach to dose justification.

Discussion:

The Agency suggested that the Sponsor consider evaluating two dose levels in the non-inferiority trial in patients with breast cancer (10 and 20 mgs). The Agency also suggested the Sponsor update their dose response and PK/PD modeling analysis using all available data.

The Agency also recommended the Sponsor conduct a small comparative PK,PD study comparing the PK, PD and safety properties of the phase 2 formulation and the phase 3 formulation.

Question 8: **Dose the agency concur the sample size calculation?**

FDA Response to Question 8:

No, FDA does not agree with the non-inferiority (NI) margin proposal, so the sample size calculation is not acceptable.

Please provide justification for NI margin, based on the proposed primary efficacy endpoint. To develop a non-inferiority criterion, a reliable estimate of the active control effect should be computed from a meta-analysis of previous controlled randomized trials. The criteria should also consider the historical between trial variability in this disease setting. Please describe how the active control effect size is estimated (the randomized trials used, analysis used, description of patient populations, selection of studies for the meta-analysis, and how these studies were selected).

For more details of the NI discussion, please refer to FDA guidance for Industry Non-Inferiority Clinical Trial:
http://www.fda.gov/downloads/Drugs/.../Guidances/UCM202140.pdf

You need to provide a method for the multiplicity adjustment.

Updated Generon Meeting Materials Submitted 10/31/15

The non-inferiority (NI) margin (b) (4) proposed in this study was based on (b) (4)

(b) (4)

(b) (4)

This NI margin has been utilized and accepted by the Agency in many recent GCSF studies and is clinically relevant for this proposed clinical study.

Updated Question 8: Dose the Agency concur with this justification?

FDA Response

FDA noted (b) (4) Since the proposed study uses Neulasta as the comparator arm, a margin (b) (4) will not be adequate. FDA recommends (b) (4) Please justify the proposed non-inferiority (NI) margin per the previous comments from the agency.

Discussion:

The Agency suggested that the Sponsor submit a Statistical Plan so that the statistical team can evaluate their latest proposal.

Question 10: **The Second Phase III Clinical Protocol: Does the agency concur with this design?**

FDA Response to Question 10:

A placebo controlled comparison with the first cycle and subsequent cycles with F-627 is acceptable; however, an improvement of (b) (4) days of severe neutropenia is not clinically meaningful. In the original approval of filgrastim there was a > 3 day difference between G-CSF and placebo.

You have not justified your flat dose. Refer to response to question # 5.

Updated Generon Meeting Materials Submitted 10/31/15

Sponsor agrees with the agency that (b) (4) days' difference between F-627 and placebo may not be large enough to be considered a clinically meaningful difference; the clinical difference assumed as part of the sample size justification will be increased from (b) (4) days to (b) (4) days.

The duration of severe neutropenia is primarily driven by the chemotherapy regimen and tumor type. In the original approval of filgrastim referred to in the Agency's response, the 3 days' difference between GCSF and placebo was a median difference8. This study was conducted over 20 years ago in small cell lung cancer patients. Cyclophosphamide, doxorubicin and epotoside were used at that time. With the development of more active chemotherapeutic agents (platinum salts, taxanes, gemcitabine, pemetrexed) alone or in combination, which not only prolong survival but also improve Quality of Life, this therapeutic approach is now reflected in current guidelines. The chemotherapy combination of cyclophosphamide, doxorubicin, and etoposide is not commonly used at the present time. The recommended treatment for these patients is a platinum salt alone, or platinum-based combinations.
The sponsor has chosen (b) (4) with the following rationale:

(b) (4)

Sample size justification has been updated to read:

(b) (4)

Updated Question 10: Does the agency concur with this revised design?
FDA Response

No. A difference of (b) (4) days is not a clinically meaningful improvement in severe neutropenia. If it is not possible or ethically feasible to do a study with a placebo control in a patient population receiving a chemotherapy regimen associated with a clinically significant incidence of febrile neutropenia, a second non inferiority trial with an active control may be the best approach.

Discussion:

The Agency stated that it was in agreement with the new design of the superiority phase 3 trial for which a two day difference in duration of severe neutropenia would be considered a clinically meaningful difference and therefore is a suitable and acceptable endpoint for demonstration of superiority.

Additional Question in Updated Generon Meeting Materials Submitted 10/31/15

The sponsor would like to seek an indication which is similar to pegfilgrastim as followed:

F-627 is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Dose the agency concur the current two phase III trials design would be adequate?

FDA Response

No. See the response to questions 8 and 10. In addition Generon has not provided sufficient justification for the proposed dose of F-627 for the phase 3 trials.

Discussion: *No discussion occurred.*

3.0 OTHER IMPORTANT MEETING INFORMATION

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 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of

Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor slides

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/s/

ALBERT B DEISSEROTH
12/03/2015