CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761378Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 144550

MEETING MINUTES

Formycon AG
c/o Strategic Drug Development Services, LLC
Attention: Scott A. Oglesby, PhD
US agent
6518 Green Rise Road
Hillsborough, NC 27278

Dear Dr. Oglesby:

Please refer to your pre-investigational new drug application (PIND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for FYB203. We also refer to the teleconference between representatives of your firm and the FDA on February 15, 2023. The purpose of the meeting was to seek guidance on the content of a complete 351(k) application for the proposed indication(s) for FYB203.

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 Jacquelyn Smith, MA, Senior Regulatory Project Manager at (301) 796-1002.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Division Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Formycon AG Slides

MEMORANDUM OF MEETING MINUTES

Meeting Type:	PIND, Biosimilar
Meeting Category:	BPD Type 4
Meeting Date and Time:	February 15, 2023, 12:30-1:30 PM EDT
Meeting Location:	Teleconference
Application Number:	144550
Product Name:	FYB203
Indications:	FYB203 is being developed (b) (4) for US-licensed Eylea
Sponsor Name:	Formycon AG

FDA ATTENDEES

Charles Ganley, MD	Director, Office of Specialty Medicine (OSM) [Division of Imaging and Radiation Medicine (DIRM), Division of Ophthalmology (DO); OND Compounding Review Team]
Alex Gorovets, MD	Deputy Director, OSM/DIRM/DO/OND Compounding Review Team
Wiley Chambers, MD	Director, Division of Ophthalmology/ Office of Specialty Medicine (DO/OSM)
Rhea Lloyd, MD	Clinical Team Leader, DO/OSM
Martin Nevitt, MD	Clinical Reviewer, DO/OSM
Michael Moses, PhD	Biologist, CDER/OPQ/OBP/DBRRI
Riley Myers, PhD	Lead Biologist, CDER/OPQ/OBP/DBRRI
Diana Willard	Chief, Project Management Staff, Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Specialty Medicine (DROSM)
Jacquelyn Smith, MA	Senior Regulatory Project Manager, ORO/DRO
Greg Soon, PhD	Statistics Team Leader, Office of Biostatistics/Division of Biometrics IV (OB/DBIV)
Abel Eshete, PhD	Statistician, OTS/OB/DBIV
Ping Ji, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)
Amit Somani, PhD	Senior Clinical Pharmacology Reviewer, OTS/OCP/DIIP
Michele Luo, MD, PhD	Scientific Reviewer, OTBB, OND

Thomas Herndon, MD	Scientific Reviewer, OTBB, OND
Sofanit Getahun, PharmD	Safety Evaluator, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis I (DMEPA I)

SPONSOR ATTENDEES

Dr. Sigrid Balser	Vice President, Clinical Development & Operations
Dr. Stefan Glombitza	Chief Executive Officer
Dr. Andrea Seidl	Chief Scientific Officer
Dr. Florian Strohmaier	Vice President Regulatory Affairs & Quality Management
Dr. Theodor Tiko	Senior Manager Regulatory Affairs
Dr. Michael Trieb	Senior Director Regulatory Affairs

(b) (4)

1.0 BACKGROUND

The meeting request, including meeting package, was submitted by the sponsor on October 13, 2022. FDA sent preliminary comments to the sponsor on February 1, 2023. After receipt of the preliminary comments, the sponsor requested to discuss questions 5, 13 and 15. The Agency's preliminary comments to the questions, the meeting discussion, and the slides (attached) are included the meeting minutes.

2.0 DISCUSSION

Question 1: (b) (4)

(b) (4)

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(b) (4)

No discussion needed.

Question 2: Documents in module 1

Does FDA agree that the proposed documents and their location in module 1 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required

Agency Response: *The Agency has not identified any issues with your proposal; however, a determination of whether the application is complete can only be made after submission of the BLA.*

No discussion needed.

Question 3: Documents in module 2

Does FDA agree that the proposed documents and their location in module 2 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.

Agency Response: *The Agency has not identified any issues with your proposal; however, a determination of whether the application is complete can only be made after submission of the BLA.*

No discussion needed.

Question 4: Extrapolation of Indications

Does FDA agree with the proposed location for the justification of extrapolation of indications?

Agency Response: *No objection.*

No discussion needed.

Question 5: Clinical Summary

Does FDA agree with the proposed approach of presenting only the clinical information from our Magellan safety and efficacy study in module 2.7 while not repeating published information from the reference product?

Agency Response: *The Agency agrees with presenting only the clinical information from the Magellan safety and efficacy study in module 2.7 and not repeating published*

information from the reference product; however, the completed Magellan study should be (b) (4)

Meeting Discussion: Questions 5, 13 and 14

(b) (4)

The Agency clarified that the protocol to evaluate similarity with US-licensed Eylea was a study of 433 patients. (b) (4)

FDA requested data from all patients be included in the study, in support of the initial BLA. The planned primary analysis was a mixed model for repeated measure (MMRM) using data through Week 24. (b) (4)

In summary, the submission of the initial BLA submission should include all efficacy, safety, PK, and immunogenicity data of all 433 treated patients collected up until Week 24. Adverse events, discontinuation for any reason, and death cases should be reported until the time of database lock in the initial BLA. The Day 120 safety update should provide the results of key efficacy, safety, and immunogenicity over the whole 56-week study period.

Post Meeting:
As discussed during the meeting, the sponsor requested confirmation that their understanding of the expectations for their BLA submission and the D120 safety update were correct.

Question 6: Nonclinical Written and Tabulated Summaries
Does FDA agree with the proposed approach of presenting only nonclinical information from studies done in conjunction with the development of FYB203 in module 2.6 and not include studies done for the RP only?

Agency Response: We agree with your proposal.

No discussion needed.

Question 7: Documents in module 3

Does FDA agree that the proposed documents and their location in module 3 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.

Agency Response: The proposed location of the data and information specified in Table 3 appears reasonable. See additional CMC microbiology comments near the end of this document.

No discussion needed.

Post-meeting comment:

To facilitate the Agency's review of the manufacturing processes for FYB203 DS and DP, provide information for all process parameters and 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 to Module 3.2.R as a single document.

Title: INSERT UNIT OPERATION

Process Parameter/Operating Parameter/ In-Process Control[1]	Proposed Range For Commercial Manufacturing[2]	Criticality Classification[3]	Characterized Range from Process Development[2]	Manufactured Range from Historical Experience[4]	Manufactured Range Assessed during Process Valdiation[5]	Justification of the Proposed Commercial Acceptable Range[6]	Comment[7]

[1] Terminology should be adapted to those used by Formycon AG
[2] As applicable
[3] For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[4] Manufacturing experience for the DP lots, and associated DS lots, which were used in the clinical studies to establish product safety and efficacy profile (i.e., pivotal clinical studies).
[5] Operation ranges, not the acceptance criteria, used during process validation.
[6] This could be a brief verbal description (e.g., "development range", "validation range", or "historical manufacturing experience", etc.) or links to the appropriate sections of the eCTD containing supporting information and data.
[7] Optional.

Question 8: Presentation of excipient information in 3.2.S.2.3

Does FDA agree with the proposed approach to include information about excipients in dossier section 3.2.S.2.3 – Control of materials?

Agency Response: No, we do not agree. Information on excipients should be provided in Section 3.2.P.4. This information may be duplicated in Section 3.2.S.2.3.

No discussion needed.

Question 9: (b) (4)

(b) (4)

No discussion needed.

Question 10: Secondary Packaging site information in 3.2.P.3.1
Does FDA agree that the packaging activities carried out at the secondary packaging site based on 21 CFR 211 GMP do not require additional information

(b) (4)

Agency Response: *No.* (b) (4)

No discussion needed.

Question 11: Warehouse information in 3.2.P.3.1

Does FDA agree that no information on warehouse/distribution hub is needed to be presented in the dossier from where drug product is distributed to the US market after QA release?

Agency Response: It is not clear if your warehouse is also used to store drug product under quarantine prior to a disposition decision. If so, the warehouse information should be reported on Form FDA 356h and Module 3 of the BLA. Refer to 2019 FDA Guidance for Industry "Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers" at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and for more information.

No discussion needed.

Question 12: Documents in module 4

Does FDA agree that the proposed documents and their location in module 4 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.

Agency Response: We agree with your proposal.

No discussion needed.

Question 13: Documents in module 5

Does FDA agree that the proposed documents and their location in module 5 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.

Agency Response: The completed Magellan study should be submitted, (b) (4) *.*

See Meeting Discussion under Question 5.

Question 14: Clinical Study Report and Study Data package

Does FDA agree that the clinical package based on the US (b) (4) **-week CSR, as indicated, to be provided in the BLA is complete and adequate for review?**

Agency Response: *No.* [redacted] (b) (4)

See Meeting Discussion under Question 5.

Additional CMC Microbiology comments:
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(k) BLA submission.

All facilities should be registered with the FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). 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.

The CMC Drug Substance section of the 351(k) 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(k) 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 (differential pressure if a peristaltic pump is used), 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.
- Parameters for filling and capping for the vials.
- 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.
- Validation of capping parameters, using a container closure integrity test.

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.
- 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.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	March 17, 2023

4.0 ADDITIONAL 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 a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

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

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

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

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[4]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov.

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

It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed Prescribing Information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d)[5] and 201.57[6] including the Pregnancy and Lactation Labeling Rule (PLLR). As you develop your proposed PI, we encourage you to review the labeling review resources on the following websites:

- *Biological Products – Specific Labeling Resources*[7] which includes the guidance for industry*: Labeling for Biosimilar Products* (July 2018).
- *Prescribing Information Resources*[8]

For other prescription drug labeling resources such as those for FDA-approved patient labeling, carton and container labeling, labeling databases, and product databases, visit *FDA's Labeling Resources for Human Prescription Drugs* website.[9]

- 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

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

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

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

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

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

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*.[10]

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

NONPROPRIETARY NAME

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

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

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

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

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*

[10] 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.

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*.

5.0 ATTACHMENTS AND HANDOUTS

Attachment: Meeting Slides

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/s/

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