CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218643Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 145052

MEETING MINUTES

American Genomics, LLC
Attention: Martin Uram
CEO
486 S. Beach Rd
Hobe Sound, FL 33455

Dear Martin Uram:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Articaine Sterile Topical Ophthalmic Solution. We also refer to the meeting between representatives of your firm and the FDA on October 23, 2023. The purpose of the meeting was to discuss the development of Articaine Sterile Topical Ophthalmic Solution.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, please contact Ahmed Ayodeji, PharmD, at 301-837-7390.

Sincerely,

{See appended electronic signature page}

Ahmed Ayodeji, PharmD
Regulatory Project Manager
Ophthalmology
Division of Regulatory Operations for Specialty Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 23, 2023, 1:00 – 2:00 PM EST
Meeting Location:	Teleconference
Application Number:	145052
Product Name:	Articaine Sterile Topical Ophthalmic Solution (AG-920)
Indication:	ocular surface anesthesia including intraocular injections
Sponsor Name:	American Genomics, LLC
Regulatory Pathway:	505(b)(2) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Wiley Chambers, MD
Meeting Recorder:	Ahmed Ayodeji, PharmD

FDA ATTENDEES

Wiley Chambers, MD	Director, Division of Ophthalmology/Office of Specialty Medicine (DO/OSM)
William Boyd, MD	Deputy Director, DO/OSM
Jenna Hammer, MD	Clinical Reviewer, DO/OSM
Kimberly Hatfield, PhD	Supervisory Toxicologist, Division of Pharmacology and Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM)
Erin Ruhland, PhD	Non-Clinical Reviewer, DPT-RPURM/SM
Guoxing Soon, PhD	Statistics Team Leader, Office of Biometrics/Division of Biometrics IV (OB/DBIV)
Yunfan Deng, PhD	Statistics Reviewer, OB/DBIV
Ping Ji, PhD	Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)
Selim Fakhruddin, PhD	Clinical Pharmacology Reviewer, OCP/DIIP
Chunchun Zhang, PhD	Senior Pharmaceutical Quality Assessor, Office of Pharmaceutical Quality/Division of New Drug Products/New Drug Products Branch VI
Milton Sloan, PhD	Pharmaceutical Quality Reviewer
Bindi Nikhar, MD	Associate Clinical Director, Office of Combination Products, OCPP, OC

Diana Willard	Chief, Project Management Staff, Office of Regulatory Operations/Division of Regulatory Operations for Specialty Medicine (ORO/DROSM)
Ahmed Ayodeji, PharmD	Regulatory Project Manager, ORO/DROSM

SPONSOR ATTENDEES

Martin Uram, MD	Chairman, American Genomics, LLC Retinal surgeon
[redacted] (b) (4)	Consultant Chemistry, Manufacturing and Controls
[redacted] (b) (4)	Consultant, Nonclinical Development
[redacted] (b) (4)	Clinical and Regulatory Consultant
[redacted] (b) (4)	Project Management Consultant

BACKGROUND

On August 2, 2023, American Genomics, LLC. (American Genomics) submitted a meeting request to discuss the development of this product. The Agency sent a Meeting Request Granted letter to American Genomics on August 21, 2023.

DISCUSSION

The questions outlined from the submitted Meeting Package are presented in **bold** font, our responses are in *italic* font. Meeting Discussion is in normal font.

Question 1:

The Sponsor has provided information on the control of the Drug Substance (DS), Articaine Hydrochloride, USP, (Active US DMF [redacted] (b) (4)). The Sponsor believes that the Release Specification, Stability Specification, and the controls are adequate to support the planned NDA. Does the FDA agree?

FDA Response:

Yes, your plan to reference DMF [redacted] (b) (4) for the drug substance information, release specification and stability specification are acceptable. The following information should be included in the NDA:

- *Authorized reference to the applicable DMF*
- *A brief section on the structure and general properties of the drug substance. This information on chemical structure and physicochemical properties critical to drug product performance will support Section 10 Description of the proposed drug product labeling.*
- *The drug substance specification from the drug substance manufacturer and the NDA regulatory specification from the drug product manufacturer as per 21 CFR*

211.84 (requires that the drug product manufacturer conduct testing of each drug substance batch as per specification upon receipt of the batch), with information to support any additional or different quality attribute/acceptance criteria.

- *Batch analysis data of three representative batches of the drug substance used in the drug product manufacture (e.g., drug product stability batches) available in the Certificates of Analysis (CoA) from the drug substance manufacturer and from the testing by the drug product manufacturer upon receipt of each batch.*
- *Information on impurities as per ICH M7 as appropriate for the drug product (use duration, population), and comparability information on the commercial drug substance and the drug substance used in the pivotal clinical studies if there is any significant difference in the synthesis, manufacturing process, or manufacturing facility.*
- *Retest period of the drug substance, if any, that is implemented by the drug product manufacturer and supported by stability data.*

***Additional comments**:*

1. (b) (4)

2. *The Electronic Submissions Gateway (ESG) has been updated to accept chemical structures as structure-data (SD) files (https://pubs.acs.org/doi/10.1021/ci00007a012). Please provide all chemical structures (i.e., drug substance, starting materials, intermediates, and impurities) in a single, comprehensive SD File in 3.2.S.3.2 to facilitate efficient review of your NDA. The SD file should include the structure of the drug substance, the structure of each other chemical, the name or abbreviation of each chemical as it appears in the NDA, and a unique identifier for cross-reference (e.g., Structure 1, Structure 2, etc.). The following data items may also be included if available: UNII code (https://precision.fda.gov/uniisearch), CAS number, role of chemical (e.g., active ingredient, process impurity, degradant, metabolite, starting material, intermediate). Please refer to the Quick Guide to Creating a Structure-Data File (SD File) for DMF Submissions for column definitions: https://www.fda.gov/drugs/drug-master-files-dmfs/drug-master-file-dmf-submission-resources. If you have a complex substance that requires additional data elements to describe, you can obtain a UNII for the substance by contacting FDA-SRS@fda.hhs.gov.*

Discussion: No Discussion.

Question 2:
The Sponsor has provided information on the Drug Product (DP) produced at Woodstock Sterile Solutions (Woodstock, IL). The DP is produced in sterile, single-dose blow-fill-seal (BFS) vials for topical ophthalmic administration. The Sponsor believes that the proposed Release and Stability Specifications are appropriate to support the planned NDA. Does the FDA agree?

FDA Response:
The proposed drug product release and stability specifications in Table 18 of the briefing package appear appropriate for the dosage form. However, additional tests (b) (4) *may be required based on the evaluation of the data presented for a regulatory approval.*

Discussion: No Discussion.

Question 3:
In Section 3.2.P.5.1 of the IND 145052, the Sponsor Specification for the DP development and clinical batches produced at Woodstock Sterile Solutions included endotoxin and drop size. The Sponsor believes that endotoxin testing is not required for topical ophthalmic products and has removed this requirement from the release and stability DP Specification for subsequent lots. The Sponsor intends to retain drop size testing for all Good Manufacturing Practice (GMP) batches. Does the FDA agree with this approach?

FDA Response:
We agree, the approach appears reasonable.

Discussion: No Discussion.

Question 4:
Due to regulatory restrictions at (b) (4) **the Sponsor performed method transfers to** (b) (4) **to allow testing at both facilities. Since those transfers were completed, the Official Action Indicated at** (b) (4) **has been resolved. The Sponsor intends to include both** (b) (4) **locations in the NDA as redundant, acceptable testing locations. Both locations will be qualified as approved vendors for the Sponsor. However, the** (b) (4) **location outsourced osmolality testing to** (b) (4) **which announced the facility closure** (b) (4)**. Batch release testing as well as 1-month and 2-month stability testing has already been performed by** (b) (4)**. The Sponsor reverted testing to** (b) (4) **as of the 3-month testing.** (b) (4) **had been qualified by** (b) (4) **prior to the outsourced testing. The Sponsor believes the data generated by** (b) (4) **to be valid for the NDA submission but recognizes that no Prior Approval Inspection activities**

will be possible at the [redacted] (b) (4) location. Rather, data is stored at [redacted] (b) (4) and can be inspected at the [redacted] (b) (4) location. Does the FDA concur?

FDA Response:
It is not clear that at the time of NDA submission you will provide 12 months stability data for the qualified commercial testing site. We expect a minimum of 12 months. If analytical methods are transferred, include the complete methods transfer package in the NDA submission.

Discussion: No Discussion.

Question 5:
In 2021, Woodstock Sterile Solutions manufactured three (3) DP batches which were to be used for both NDA Registration and Process Validation purposes. Upon batch documentation review, it was discovered that only one unique lot of DS had been used to produce all 3 DP batches. The Sponsor recognizes that ICH Q1A(R2) Section 2.2.3 indicates that "where possible, batches of the drug product should be manufactured by using different batches of the drug substance". Therefore, two (2) additional DP lots were manufactured in 2022 using two (2) unique lots of DS to be used for NDA Registration. At the time of the proposed NDA submission, the Sponsor expects to have a minimum of 18 months stability on the original 3 DP batches (manufactured in 2021) and at least 9 months stability on the additional 2 DP batches (manufactured in 2022). Additionally, the Sponsor has 36 months stability data on the Phase 3 Clinical Batch (Lot 01219B). All data for the supporting stability study on Lot 01219B was found to be within specification throughout the 36-month stability period. The Sponsor recognizes that ICH Q1A(R2) Section 2.2.7 indicates that the "long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission…". The Sponsor believes that although the original 3 batches of DP were manufactured with the same lot of DS, those 3 DP batches in combination with the subsequent 2 DP batches would satisfy the overall intention of the guideline, provided all testing met the acceptance criteria in the proposed Specification. Additionally, the Sponsor would commit to providing the FDA with the 12-month stability data for the 2 DP batches manufactured in 2022 during the FDA review period for the NDA. Does the FDA concur with this submission approach?

FDA Response:
Your approach is acceptable; however, review of all data submitted after the initial submission will be reviewed at FDA's discretion.

Discussion: No Discussion.

Question 6:
Woodstock Sterile Solutions has performed container-closure integrity testing (CCIT) as part of the qualification of the BFS mold/container and includes this qualification as an integral part of their sterility assurance validation program for BFS manufacturing. CCIT is not included in the DP stability program but rather sterility testing is performed at release, annually, and at the conclusion of the stability study. The Sponsor believes that although CCIT *could* be conducted in lieu of sterility testing (FDA Guidance Container and Closure System Integrity Testing *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products, February 2008) it is not a mandatory requirement and is therefore not included in the DP stability program. Does the FDA agree that CCIT is not required to be conducted on stability for this DP based on the testing requirements within the current stability program?

FDA Response:
We agree that CCIT is not required during stability because the stability program includes sterility testing. However, because the sterile product is filled in blow-feal-seal (BFS) units, we recommend leak testing of 100% of BFS units prior to release. Note that sufficient container closure integrity testing data will be needed to assess the adequacy of the container closure system, which will be assessed during the New Drug Application review cycle.

Discussion: No Discussion.

Question 7:
Extractables & Leachables (E&L) testing on the primary container closure system, including the BFS vials and the foil pouch was performed. The E&L program included the following studies prior to performing leachables testing on stability of 3 DP batches through expiry:

a. **Controlled extraction screening on inorganic elemental impurities on the foil** (b) (4) **foil to represent to-be-marketed ink) and on the BFS resin.**
b. **Volatile compounds and residual solvents characterization of the foil and the resin using headspace gas chromatography-mass spectrometry (HS GC-MS) with electron ionization.**
c. **Semi-volatile compounds characterization of the foil and resin using gas chromatography mass-spectrometry (GC-MS) with electron ionization.**
d. **Non-volatile/polar compound characterization of the foil and resin using high performance liquid chromatography-ultraviolet-mass spectrometry (HPLC-UV-MS) with positive and negative atmospheric pressure chemical ionization and diode array detector.**
e. **Leachable elemental impurities screening of the drug product in the container-closure system (BFS resin and foil pouch).**
f. **Organic leachables characterization on stressed drug product (9.8-week storage in 65°C to represent 3-year long-term storage based on the**

Arrheniuequation) using the methodology described in items c, d, and e above. Limit of detection is (b) (4) part per million (ppm) and limit of quantitation is (b) (4) ppm.

g. Risk assessment evaluations.

h. The Sponsor does not expect to include adhesive labeling in the to-be-marketed DP. Therefore, adhesives were not included in the E&L program.

Does the FDA agree that this E&L program is acceptable to support the planned NDA?

FDA Response:

Yes, we agree with your program approach and rationale. A complete report on the testing method development and findings should be included in the NDA submission. Refer to USP <1663>, <1664> for additional recommendations. Any impurities found must be adequately controlled, those found above the applicable thresholds should be adequately qualified.

Discussion: No Discussion.

Question 8:

Sponsor has data from a single 14-day study comparing pouched and unpouched product exposed to ambient environment which indicates 14-day exposure does not alter the stability of the product. Additionally, a photostability study conducted per ICH Q1B Option 2 Photostability conditions was conducted on un-pouched samples. Are these studies sufficient to support a statement on the product labeling (b) (4) If not, what would be the expectation to support this claim?

FDA Response:

The proposed in-use study plan should include assessment of all changes in parameters that could happen upon opening. The adequacy of the assessment will be evaluated at NDA review. The in-use study should simulate the use of the product in practice with regard to both labeled usage and storage conditions. The parameters tested prior to opening should be monitored to determine the impact of opening i.e., appearance, assay, pH, etc. A study duration out to 30 days is recommended. If the recommended storage conditions (e.g., temperature) does not change, and the testing does not demonstrate any differences, the out of pouch time is recommended to be half of the testing period. We recommend long term testing of the product without the pouch.

Discussion: The Agency emphasized that the in-use study data would need to be twice the duration proposed in labeling.

Question 9:

Given the minimal space on each individual BFS vial, the Sponsor proposes to include only the following information on each vial: "(b) (4) American Genomics, Lot [#], Exp [Date]", where the [ ] represents a variable data field unique to each lot produced. Does the FDA agree this is acceptable content for embossed labeling of the individual BFS vials? If not, what does the FDA suggest must be included?

FDA Response:
The proposed content appears adequate.

Discussion: No Discussion.

Question 10:
The Sponsor believes that the nonclinical pharmacology, pharmacokinetics, and toxicology studies conducted, reported, and previously submitted in SN 0001 and SN 0011 are adequate for acceptance for review of the NDA, and to support the intended application for approval. Does FDA concur?

FDA Response:
We agree.

Discussion: No Discussion.

Question 11:
The Sponsor believes that biocompatibility studies are not required for this product. The drug product is packaged in a standard low-density polyethylene (LDPE) BFS vial commonly used in approved topical single-dose ocular products. Furthermore, the pivotal nonclinical ophthalmic toxicology studies in rabbits used the to-be-marketed LDPE BFS container-closure and an extensive E&L program was conducted for the drug product in the proposed commercial packaging (as defined in Question 7). Does the FDA concur that no biocompatibility studies are required?

FDA Response:
From the nonclinical perspective, we agree.

Discussion: No Discussion.

Question 12
The Sponsor provides the results of pivotal, Phase 3 studies of the safety and efficacy of AG-920 Sterile Topical Ophthalmic Solution 8% (AG-920-CS301 and AG-920-CS302). The subjects in this study were healthy individuals, and efficacy was assessed by a conjunctival pinch test. The Sponsor believes these two confirmatory studies are adequate for acceptance for review of the NDA and to support the intended application for approval. Does FDA concur?

FDA Response:
We have no objection; however, whether these two studies are adequate will be a review issue.

Discussion: No Discussion.

Question 13:
Efficacy: Statistical analysis: Further on above question, the Sponsor notes that the primary efficacy analysis of the primary endpoint (i.e., the proportion of subjects with no pain at 5 minutes) was conducted using a Pearson chi-square test for AG-920-CS301 and a Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for study eye (OD vs OS) for AG-920-CS302. This was based upon an imbalance in right eyes and left eyes in the CS302 study. As both analyses provide equivalent information, no additional statistical analysis is planned for the NDA. Does FDA concur?

FDA Response:
We have no objection; however, we may request you conduct additional analyses during the review process.

Discussion: No Discussion.

Question 14:
The Sponsor conducted all clinical studies with the 8% concentration of AG-920. This decision was made based primarily on nonclinical and chemistry data. The Sponsor believes that this is the optimum concentration and does not intend to conduct any dose-response studies in humans. The Sponsor believes this is adequate for acceptance for review of the NDA, and to support the intended application for approval. Does FDA concur?

FDA Response:
While we strongly encourage exploration of multiple concentrations, identification of the optimal concentration is not a legal requirement for approval.

Discussion: No Discussion.

Question 15:
In addition to the Phase 3 safety and efficacy studies (AG-920-CS301 and AG-920-CS302), the Sponsor conducted a double-masked, vehicle-controlled safety study, AG-920-CS303, in which 166 subjects received the intended marketed dose of AG-920 Sterile Topical Ophthalmic Solution. There were no safety issues. The total number of subjects exposed to AG-920 Sterile Topical Ophthalmic Solution across all 5 clinical studies was 330 (each receiving the intended marketed dose of two drops in the study eye). The Sponsor believes this is adequate clinical

safety exposure for acceptance for review of the NDA, and to support the intended application for approval. Does FDA concur?

FDA Response:
We have no objection, however, whether this is adequate to support approval will be a review issue.

Discussion: *No Discussion.*

Question 16:
Safety: In Study AG-920-CS303, a parallel, unequal randomization (2:1) vehicle-controlled study, specular microscopy was performed pre-dose and 3 months post-dose in 16 subjects following a single clinical dose (two drops in the study eye). The mean change in endothelial cell density was -23.83 ± 92.18 cells/mm^2 in the 13 subjects in the AG-920 treatment group and was -44.33 ± 85.19 cells/mm^2 in the 3 subjects in the vehicle treatment group (p = 0.6736). There was little or no change in other measures of corneal structure. The Sponsor believes that they have met the requirement to evaluate this safety measure, and there is no safety concern. Does FDA concur?

FDA Response:
Testing in less than 100 subjects treated with proposed product is not considered adequate testing to evaluate corneal endothelial safety.

Discussion: America Genomics stated that since the time of the PIND meeting, two GLP preclinical studies have been performed, and Study AG-920-CS303 included 13 individuals dosed with AG-920 who completed the 90-day post-dose evaluation with no safety concerns.

The Agency responded that 13 subjects does not provide a reasonable evaluation of the corneal endothelium. The Agency stated that it will review the data when the NDA is submitted. The Agency expects to review corneal endothelial cell data either with the NDA or as a Post-Marketing Requirement.

Question 17:
Clinical pharmacology: The Sponsor conducted a study (AG-920-CS101) in 14 healthy volunteers who received AG-920 Sterile Topical Ophthalmic Solution as a single dose (two drops, 30 seconds apart) in the study eye. For articaine, the mean C_{max} of 5.423 ng/mL was reached at a median T_{max} of 0.250 hours. The overall exposure was under 7 ng*hr/mL. The mean $t_{½}$ was approximately 1.5 hours. For the metabolite, articainic acid, the mean C_{max} of articainic acid of 21.34 ng/mL was reached at a median T_{max} of 1.001 hours. The overall exposure was approximately 10-times greater than the parent at approximately 63-67 ng*hr/mL. The mean $t_{½}$ was approximately 2.3 hours. The Sponsor believes that this meets the requirements for evaluating systemic exposure to AG-920 and to its principle

inactive metabolite, articainic acid. The Sponsor believes this is adequate for acceptance for review of the NDA, and to support the intended application for approval. Does FDA concur?

FDA Response:
The study described in this question is sufficient for review of the proposed NDA, the adequacy of the data will be determined upon review of the NDA.

Discussion: *No Discussion.*

Question 18:
Pediatric: The Sponsor conducted Study AG-920-CS304, consistent with the approved initial Pediatric Study Plan (PSP). The primary objective of this study was to evaluate the anesthetic efficacy of AG-920 in a pediatric population. The primary efficacy endpoint was whether the investigator was able to perform the eye examination. In all subjects in each treatment group, the investigator was able to perform the eye examination without additional local anesthetic. Investigators were also asked a subjunctive question about whether they judged anesthesia adequate to perform the examination. The response to this question showed greater efficacy for the positive control, marketed proparacaine, than for AG-920. There were no adverse events, and no changes observed in biomicroscopy in either the AG-920 or proparacaine treatment group. As a result of meeting the primary and secondary endpoints of the study per protocol, the Sponsor believes that they have met the requirement of the PSP. Does FDA concur?

FDA Response:
The study described in this question is sufficient for review of the proposed NDA. The adequacy of the data will be determined upon review of the NDA.

Discussion: No Discussion.

Question 19:
The Sponsor intends to provide a set of Analysis Data Model (ADaM) and SDTM Study Data Tabulation Model (SDTM) datasets and corresponding documentation for the three Phase 3 clinical studies and believes this will meet FDA's requirements. Does FDA concur?

FDA Response:
Agree.

Discussion: No Discussion.

Question 20:
Integrated Summaries:

A. In the NDA, the Sponsor intends to summarize the clinical efficacy of AG-920 Sterile Topical Ophthalmic Solution in Module 2.5 and 2.7 based upon individual study results (i.e., no combined analysis of efficacy). The Sponsor does NOT intend to prepare an Integrated Summary of Efficacy (ISE), nor conduct any combined statistical analysis of studies, nor to analyze efficacy by subject pre-study characteristics. Does FDA concur?

B. The Sponsor intends to prepare an Integrated Summary of Safety (Module 5.3.5.3) in which the safety for all conducted clinical studies is provided. As the primary adverse event summary intended for the package insert, the Sponsor intends to combine the 3 phase 3 studies (AG-920-CS301, CS302, and CS303). While results from the pediatric study (AG-920-CS304) and the clinical pharmacology study (AG-920-CS101) will be provided, they will not be combined with the Phase 3 studies. The Sponsor does not plan to analyze safety by subject pre-study characteristics. Finally, the Sponsor does NOT plan to submit a diversity plan. Does FDA concur?

FDA Response:
Agree, provided the demographics of all subjects enrolled in the clinical trials is provided.

Discussion: American Genomics agreed to provide the demographics of all subjects enrolled in the clinical trials in the ISS. The Agency indicated that studies AG-920-CS301 and AG-920-CS302 would be required for the purposes of BIMO. The Agency clarified that BIMO are usually a separate datasets.

Question 21:
Package insert:

A. Indication: The Sponsor intends to state the indication as: (b) (4) [redacted] (b) (4) [redacted]

B. Safety: The adverse event section of the package insert will be based upon the three Phase 3 studies (AG-920-CS301, AG-920-CS302 and AG-920-CS303).

C. Pediatric: The Sponsor intends to include the following pediatric labeling in the package insert: (b) (4) [redacted]

Does FDA concur?

FDA Response:
It is premature to answer this question until the studies are submitted and reviewed in the NDA. Specific information in the package insert will be a review issue.

Discussion: *No Discussion.*

Question 22:
Package insert: (b) (4)

Does FDA concur?

FDA Response:
No. (b) (4)

Discussion: No Discussion.

Question 23:
To address issues of safety (nonclinical and clinical) for this molecule outside of the Sponsor's research, the Sponsor plans to conduct an updated literature search using the same database (PubMed) and search strategy (articaine AND "safety" OR "toxic") as performed in the IND annual reports. Relevant publications will then be reviewed for safety. Does FDA concur that this will meet the Sponsor's obligations?

FDA Response:
No objection.

Discussion: No Discussion.

Question 24:
At this time, the Sponsor has not selected a brand name. The Sponsor may submit the NDA with a placeholder brand name – e.g., "BRANDNAME". Does FDA concur?

FDA Response:
We concur. Once a proprietary name is found conditionally acceptable you may replace the placeholder "BRANDNAME" throughout the labels and labeling with the conditionally acceptable proprietary name.

Discussion: No Discussion.

Question 25:

Genus decision:

A. The Sponsor understands that based upon the 2021 Genus decision, parts of 21 CFR 200.50 regarding ophthalmic dispensers is no longer valid, and that this product will be regulated as a combination product. As the primary mechanism of action is pharmacological, we understand that CDER Division of Ophthalmology will be the primary reviewing division for this NDA. Does FDA concur?

FDA Response:

Yes, the articaine ophthalmic solution, 8% (AG-920) prefilled within the blow-fill-seal (BFS) container appears to be a single-entity combination product per 21 CFR 3.2(e)(1). We agree that based on the pharmacological Primary Mode of Action (PMOA) of the proposed AG-920 combination product, CDER would be the lead center, and the Division of Ophthalmology would be the appropriate review division.

Discussion: No Discussion.

B. The Sponsor believes that the BFS device is a class I device and is exempt from the CFR 820.30 Design Controls based on the CFR 820.1(a) *Applicability* "With respect to class I devices, design controls apply only to those devices listed in §820.30(a)(2)" and the March 2022 FDA Guidance Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4, Section III.A which states eye dropper bottles/ampules are considered to be "lower-risk device constituent parts". Does the FDA agree that CFR 820.30 Design Controls is not required for this BFS drug product?

FDA Response:

At this time, we do not agree that 21 CFR 820 is not required. However, as described in the guidance "Certain Ophthalmic Products: Policy Regarding Compliance with 21 CFR Part 4 Guidance for Industry" (March 2022), FDA is evaluating how 21 CFR part 820 requirements as set forth in Part 4 apply to combination products that include constituent parts such as unit-dose, blow-fill-seal containers/ampules that administer the drug directly to the eye. Until FDA has further considered the application of these requirements to these combination products, the Agency generally does not intend to take enforcement action with respect to noncompliance with any applicable Part 820 requirements for such approved ophthalmic products, including your product if your product is approved. When the Agency publishes its current thinking on how the part 820 requirements apply to these combination products, FDA will also address its timing expectations for application holders and manufacturers of such approved combination products to come into compliance with any applicable Part 820 requirements.

Discussion: *No Discussion.*

Question 26:

Genus decision: The Sponsor believes that Human Factors testing is not required for this product as the BFS vial is a class I device intended for use by medical professionals who are experienced in use of this type of container/closure system. No explicit, separate human factors study was conducted. Does the FDA concur that no further work is required for the approval of the NDA?

FDA Response:
We concur from a medication error perspective. You do not need to submit human factors such as a comparative analysis, use-related risk analysis, or data from a human factors validation study to support the marketing application, at this time.

Discussion: No Discussion.

ADDITONAL COMMENTS

For additional information, refer to the following two guidance documents regarding the Agency's expectations for filing an NDA submission for aseptically filled products, including blow-fill-seal products.

- *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-documentation-sterilization-process-validation-applications-human-and-veterinary-drug*

- *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. 2004. https://www.fda.gov/media/71026/download*

Discussion:
American Genomics requested confirmation that a Risk Evaluation and Mitigation Strategy (REMS) study is not required for this product. The Agency stated that a REMS is unlikely, but a final decision is made during review of the application.

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/

WILEY A CHAMBERS
11/15/2023 10:52:09 PM