CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218643Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 14, 2025
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	218643
Product Name, Dosage Form, and Strength:	Cyklx (articaine) ophthalmic solution, 8%
Applicant Name:	American Genomics, LLC
FDA Received Date:	August 13, 2025
TTT ID #:	2024-11299-2
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

1 PURPOSE OF MEMORANDUM

American Genomics, LLC submitted revised container label, foil pouch and carton labeling received on August 13, 2025 for Cyklx. The Division of Ophthalmology (DO) requested that we review the revised container label, foil pouch and carton labeling for Cyklx (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we and the Division of Ophthalmology (DO) made.[ab]

2 CONCLUSION

American Genomics, LLC implemented[c] all of our recommendations, for the container label, foil pouch and carton labeling. Additionally, the Applicant implemented DO's recommendation to include the statement *"Store unopened single-dose vials in pouch until ready for use. Discard opened vial after use"* to the foil pouch labeling, carton labeling and Section 16 of the Prescribing Information (PI).

We have no additional recommendations at this time.

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[a] Getahun, S. Review of Revised Label and Labeling for Cyklx (218643). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 AUG 12. TTT ID: 2024-11299-1.

[b] Connis, N. FDA Communication: Information Response 2 12Aug25 | NDA 218643 / American Genomics for Cyklx. Silver Spring (MD): FDA, CDER, OND (US); 2025 AUG 12. NDA 218643. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807d23e1

[c] Cover Letter 08/13/2025 – Response to Informational Request (NDA 218643 Cyklx). Hobe Sound (FL): American Genomics, LLC; 2025 AUG 13. Available from: \\CDSESUB1\EVSPROD\nda218643\0015\m1\us\12-cover-letters\cover-letter.pdf

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/s/

SOFANIT N GETAHUN
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 12, 2025
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 218643
Product Name, Dosage Form, and Strength:	Cyklx (articaine ophthalmic solution), 8%
Applicant Name:	American Genomics, LLC
FDA Received Date:	August 5, 2025
TTT ID #:	2024-11299-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

American Genomics, LLC submitted revised container label proposal, foil pouch and carton labeling received on August 5, 2025 for Cyklx. The Division of Ophthalmology (DO) requested that we review the revised container proposal, foil pouch and carton labeling for Cyklx (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

Reference is made to the Applicant's response to the Agency's information request (Appendix B). We note for two container label recommendations the Applicant states:

- *The vials will be embossed with the proprietary name. At the time of original submission, the proprietary name had not been confirmed.*
  Side 1: Cyklx American Genomics
  Side 2: Lot [#] Exp [YYYYMMM]

- *The Sponsor has reviewed 21 CFR 201.25(b)(1)(i)(F) which states:*
  "What drugs are subject to these bar code requirements? The following drug products are subject to the bar code label requirements:…"
  "Low-density polyethylene form fill and seal containers that are not packaged with an overwrap." The drug product vials are exempt from this requirement as there is a foil pouch overwrap which will contain the bar code.

(b) (4)

We maintain our position that the container label be in compliance with 21 CFR 201.10(i) small label requirements i.e., at the minimum include proprietary name, established name, identifying lot or control number, name of manufacturer, packer, or distributor of the drug. Additionally, from a medication safety perspective, we recommend including the strength to further facilitate product identification of the product.[b]

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[a] Getahun, S. Label and Labeling Review for Articaine (NDA 218643). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 MAR 24. TTT ID: 2024-11299.

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

Furthermore, we do not agree with the Applicant's interpretation of 21 CFR 201.25(b)(1)(i)(F). We note that 21 CFR 201.25(b)(1)(i)(F) lists as exempt *"Low-density polyethylene form fill and seal containers that are NOT packaged with an overwrap."* The regulation exempts containers without an overwrap, not those with an overwrap. The Applicant's vials with foil pouch overwrap would be subject to barcode requirements. However, we note the regulation also allows for exemptions, including when the barcode requirement would not be technologically feasible. Thus, we will defer the Applicant to our Office of Compliance to determine if a waiver request is warranted.

Moreover, beyond the container label concerns, the foil pouch and carton labeling can be improved from a medication safety and compliance perspective.

3 CONCLUSION

The revised container label, foil pouch and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for American Genomics, LLC in Section 3.

4 RECOMMENDATIONS FOR AMERICAN GENOMICS, LLC

A. Container Label

1. The established name is missing on the label. Per 21 CFR 201.10(i), the label must include at a minimum the proprietary name, established name, identifying lot and name of manufacturer. Additionally, per USP General Chapter <7>, the label of an official drug product shall bear the expiration date. To comply with 21 CFR 201.10(i) and USP General Chapter <7>, add the established name on the label. Additionally, from a medication safety perspective, we recommend including the strength to further facilitate product identification of the product.[c] To comply, you may choose to emboss the requested identifying product information. Please note, text that is raised or recessed (i.e., embossed) without color, on clear, transparent, or translucent containers (e.g., low-density polyethylene (LDPE) vials) is generally illegible. Alternative strategies include affixing a paper label to each tail of the blow-fill seal vial or individually wrapping each unit, among other possible strategies, so that all critical identifying product information is available throughout the entire medication use process.
2. We note that 21 CFR 201.25(b)(1)(i)(F) lists as exempt "Low-density polyethylene form fill and seal containers that are not packaged with an overwrap." However, the proposed LDPE vials are contained within an overwrap, thus the barcode

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

requirements apply. However, the regulation also allows for exemptions, including when the barcode requirement would not be technologically feasible. In order to obtain a waiver from the linear barcode requirements under 21 CFR 201.25(b)(1)(i)(ii), we recommend that you contact the Office of Compliance at CDERBarcodeQuestions@fda.hhs.gov.

B. Foil pouch and Carton Labeling

1. As currently presented, the eye graphic located in the lower half of the principal display panel competes in prominence with the critical product information on the PDP. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements (if any) should be the most prominent information on the PDP. Decrease the prominence of your eye graphic relative to the prominence of the critical information on the PDP. For example, this may be accomplished through increasing the prominence of the critical information and/or minimizing the size of the eye graphic itself or relocating it to another panel.

2. The route of administration is not present on the principal display panel. Failure to include the route of administration on the principal display panel may lead to wrong route errors. Add the route of administration "For Topical Application in the Eye" in accordance with 21 CFR 201.100(b)(3).

3. As currently presented, the product's indication is prominently displayed on the PDP. Additionally, we note the indication statement includes reference to [redacted] (b) (4) " which could be misinterpreted as the product's intended route of administration. The proprietary name, established name along with the product's strength, route of administration, and warning or cautionary statement (if any) should be the most prominent information on the PDP. Remove the indication statement.

4. Ensure the national drug code (NDC) is updated on the labeling when the final NDC is determined.

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APPENDIX B. RESPONSE TO AGENCY'S JULY 24, 2025, INFORMATION REQUEST

Response to Agency's July 24, 2025 Information Request, received on August 5, 2025 and available at: \\CDSESUB1\EVSPROD\nda218643\0014\m1\us\12-cover-letters\cover-letter.pdf

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/s/

SOFANIT N GETAHUN
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VALERIE S VAUGHAN
08/12/2025 11:18:31 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 5, 2025

To: Nick Connis, Regulatory Project Manager
Division of Ophthalmology (DO)

Shilpa Rose, Clinical Reviewer, DO

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for CYKLX (articaine ophthalmic solution) 8%, for topical ophthalmic use

NDA: 218643

Background:

In response to DO's consult request dated December 5, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for Cyklx.

PI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 25, 2025, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on January 24, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 24, 2025
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 218643
Product Name, Dosage Form, and Strength:	Articaine ophthalmic solution, 8%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	American Genomics, LLC
FDA Received Date:	October 16, 2024, November 4, 2024, December 3, 2024, January 24, 2025, and February 4, 2025
TTT ID #:	2024-11299
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 INTRODUCTION

As part of the approval process for Articaine ophthalmic solution, the Division of Ophthalmology (DO) requested that we review the proposed Articaine Prescribing Information (PI), container label, foil pouch, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Articaine is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Septocaine (Articaine hydrochloride and epinephrine), NDA 020971.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review of NDA 218643.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C
Information Request (IR)	D

3 CONCLUSION

The proposed Articaine Prescribing Information (PI), container label, foil pouch and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Ophthalmology (DO) in Section 4 and for American Genomics, LLC in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for the Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	We note discrepancy in how the established name is presented between the PI, carton, and pouch labeling versus how it appears on the container i.e., (b) (4)	The established name is important for product distinction that should be presented in a consistent manner throughout the labels and labeling.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate established name for this proposed product. We recommend the establish name is presented consistently across all labels and labeling.

Table 2. Identified Issues and Recommendations for the Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	[redacted] versus “[redacted]		
2.	The proposed proprietary name “[redacted]” is included throughout the PI.	The proposed proprietary name “[redacted]” was found unacceptable by the Agency as communicated in our February 24, 2025, Proprietary Name Request Unacceptable letter.	Replace all references to “[redacted]” with the placeholder “TRADENAME.” Once a proprietary name is found conditionally acceptable, the placeholder “TRADENAME” can be replaced with the conditionally acceptable proprietary name.
Highlights of Prescribing Information			
1.	As currently presented, the strength expressed as a percentage is not included.	Lack of consistency. The strength is expressed as 8% on the container label and carton labeling.	We recommend the strength presentation is revised to be expressed as the percentage, i.e., 8%.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The term “dose” is used to describe the “dosage” in the statement, *“The recommended dose of* [redacted] *is 2 drops applied 30 seconds apart to the ocular surface.”*	The term *dose* should be used to refer to a specific amount of drug taken at one time. However, the term *dosage* should be used when specifying the amount of drug administered at a specific frequency (and over a certain duration, if applicable). See *Draft Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.*[a]	Revise the term “dose” to “dosage” in the recommended dosage statement.

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Table 2. Identified Issues and Recommendations for the Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, information included under the following sub*sections of Section 5 Warning and Precautions:* (b) (4)	This administration information is pertinent to include in Section 2 to help reduce administration error that could affect the safety or effectiveness of the drug. See *Draft Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.*[b]	We recommend including the following statements in Section 2 of the PI: *"TRADENAME is indicated for administration under the direct supervision of a healthcare provider. TRADENAME is not intended for patient self-administration."* *"For topical ophthalmic use only. TRADENAME is Not for Injection or Intraocular Administration"* *"Advise patients to avoid touching the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye."* *"Do not touch the dropper tip to any surface as this may contaminate the product."*
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented, the appropriate information to facilitate identification of the proposed dosage form is not included.	A description of the identifying characteristics can be used to help identify the product and is required per 21 CFR 201.57(c)(4)(ii).	Include a description of identifying characteristics of the dosage form in accordance with 21 CFR 201.57(c)(4)(ii).
2.	As currently presented, the strength expressed	Lack of consistency. The strength is expressed as 8%	We recommend the strength be presented as the percentage, i.e., 8%.

[b] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Table 2. Identified Issues and Recommendations for the Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	as a percentage is not included.	on the container label and carton labeling.	
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the appropriate information to facilitate identification of the proposed dosage form is not included.	A description of the identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	Include a description of identifying characteristics of the dosage form in accordance with 21 CFR 201.57(c)(17)(iii).
2.	As currently presented, the volume of the single-dose vial is described as "0.40 mL," which includes a trailing zero.	Trailing zeros can lead to 10-fold misinterpretations.	Revise "0.40 mL" to "0.4 mL."
3.	The strength i.e., 8% is not included.	The strength is required per 21 CFR 201.57(c)(17). Lack of consistency. The strength is expressed as 8% on the container label and carton labeling.	Add the strength in accordance with 21 CFR 201.57(c)(17).

5 RECOMMENDATIONS FOR AMERICAN GENOMICS, LLC

Table 3. Identified Issues and Recommendations for American Genomics, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label, Pouch, and Carton labeling			
1.	The proposed proprietary name "(b) (4)" is included on the labeling.	The proposed proprietary name "(b) (4)" was found unacceptable by the Agency as communicated in our February 24, 2025, Proprietary Name Request Unacceptable letter.	Remove the proposed proprietary name "(b) (4)" from the labels and labeling. Additionally, please note that methods used to highlight a portion of the name (e.g., Tallman lettering or different font color) are typically reserved for use when a safety

Table 3. Identified Issues and Recommendations for American Genomics, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			concern has been identified that necessitates additional mitigation strategies. Once a proprietary name is found conditionally acceptable, please take the above into consideration when designing how the proprietary name will appear on the labels and labeling.
Container Label			
1.	As currently presented, the format for the expiration date is not defined on the container label.	We are unable to assess the proposed expiration date format from a medication safety perspective.	Identify the expiration date format you intend to use on the container label. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.

Table 3. Identified Issues and Recommendations for American Genomics, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*
2.	We note discrepancy in how the established name is presented between the PI, carton, and pouch labeling versus how it appears on the container i.e., "(b) (4)" versus (b) (4)	Lack of clarity. The discrepancy between labels and labeling could lead to confusion.	Revise the established name to match throughout the product's label and labeling, i.e., PI, container label, carton, and pouch labeling.
3.	We note the container label includes embossed information as: Side 1: (b) (4) and American Genomics Side 2: Lot [#], and Exp [Date]. However, it does not include the proprietary name nor linear barcode.	The proprietary name is part of the minimum information that is required per 21 CFR 201.10(i) and is important for product distinction. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Additionally, from a medication error perspective, we note that information embossed on	We recommend affixing a label to the tail of the vial or individually wrapping the vials to ensure all minimum required product information is legible[d] and present with the product up to the point of administration. Ensure the proprietary name of the drug is included on the container (vial) label in accordance with 21 CFR 201.10(i). Additionally, ensure the product's linear barcode is included in accordance with 21 CFR 201.25(c)(2).

[d] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 3. Identified Issues and Recommendations for American Genomics, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		clear plastic such as Low-density polyethylene (LDPE) containers without color is generally illegible making it difficult to read, which can lead to medication errors (e.g., wrong drug errors) in instances where the plastic LDPE vial is stored separated from the pouch or carton labeling. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)[c].	
Foil Pouch and Carton Labeling			
2.	As currently presented, we note the concentration i.e., (b) (4) is presented on the principal display panel (PDP).	Including the milligram per 1 milliliter volume concentration on the PDP for this ophthalmic solution when the container contains less than 1 mL increases the risk of misinterpreting the volume contained in each vial.	We recommend removing the concentration, (b) (4) from the PDP and retaining only the 8% strength.
3.	The storage statement on the carton and pouch labeling can be improved for clarity. Similarly, the discard statement may be improved for clarity.	We note the expiration date for the container is not intended to differ from that of the pouch or carton (e.g., a different beyond use date is not indicated once the	We recommend revising the storage statement to remove the portion stating, "(b) (4) that is present on the carton and pouch labeling, so

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 3. Identified Issues and Recommendations for American Genomics, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		container is removed from the carton or pouch). Each vial is intended to be discarded after use.	the storage statement reads as: *"Store at (b) (4) °C to 25°C (b) (4) °F to 77°F)."* Additionally, revise the discard statement to read as: *"Discard vial after use"*
4.	As currently presented, we note the net quantity is stated as, (b) (4)	The net quantity statement can be revised to provide clarity.	We recommend revising to include the volume that is in each vial. For example: a. For the carton labeling, revise to: "Contents: • Five 0.4 mL single-dose vials per pouch • Ten pouches per carton" b. For the foil pouch labeling, revise to: "Contents: • Five 0.4 mL single-dose vials per pouch" Remove the "(b) (4) statement from the pouch labeling.
5.	As currently presented, we note that the product identifier is not included.	The Drug supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	Add the product identifier to the carton labeling and identify the intended location of the 2-D data matrix barcode portion of the product identifier. Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode

Table 3. Identified Issues and Recommendations for American Genomics, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		The DSCSA guidance on product identifier recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] Serial: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]	scanners the ability to correctly read each barcode. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers* (July 2021).[e]
6.	The terminology within the statement of dosage (i.e., Usual Dosage) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	Revise the statement of dosage to "Recommended Dosage: 2 drops applied 30 seconds apart to the ocular surface."
7.	We note the unspecified placeholder for your company logo on the PDP. 	It is not clear how the presentation of the logo will affect the layout of critical product information on the PDP.	Submit revised labeling which includes the intended logo. Additionally, note that the proprietary name, established name, dosage form, product strength, route of administration, and warning or cautionary statements (if any) should be the most prominent

[e] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers

Table 3. Identified Issues and Recommendations for American Genomics, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			information on the PDP. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).[f]
8.	As currently presented, we note the cautionary statement that clarifies this product is not intended for patient self-administration is included on the side panel.	Important cautionary statements should be included on the PDP to minimize the risk of overlooking them. Additionally, when warning(s) or cautionary statement(s) are added to the container label or carton labeling, they should generally be written affirmatively.[g]	We recommend revising the cautionary statement to: "For healthcare provider administration only." Additionally, we recommend adding the cautionary statement to the PDP of the carton and pouch labeling.

[f] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

[g] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Articaine received on October 16, 2024 from American Genomics, LLC, and the Listed Drug (LD).

Table 4. Relevant Product Information for Articaine and the Listed Drug (LD).		
Product Name	Articaine	Septocaine[h] (NDA 020971)
Initial Approval Date	N/A	April 3, 2000
Active Ingredient	Articaine	Articaine hydrochloride and epinephrine
Indication	For ocular surface anesthesia prior to ocular procedures and/or intraocular injections.	Local, infiltrative, or conductive anesthesia in both simple and complex dental procedures in adults and pediatric patients 4 years of age or older.
Dosage Form	ophthalmic solution	injection
Strength	8%	•Articaine HCl 4% (40 mg/mL) and epinephrine 1:200,000 (as epinephrine bitartrate 0.009 mg/mL) • Articaine HCl 4% (40 mg/mL) and epinephrine 1:100,000 (as epinephrine bitartrate 0.018 mg/mL) • Articaine HCl 4% (40 mg/mL) and epinephrine, 1:100,000 (as epinephrine bitartrate 0.018 mg/mL)
Route of Administration	Ophthalmic	Intraoral submucosal infiltration or nerve block

[h] Septocaine [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. November 20218. [cited 2025 FEB 05]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020971s042lbl.pdf

Table 4. Relevant Product Information for Articaine and the Listed Drug (LD).		
Product Name	Articaine	Septocaine[h] (NDA 020971)
Dose and Frequency	2 drops applied 30 seconds apart to the ocular surface.	For dental procedures by intraoral submucosal infiltration or nerve block. - For infiltration: 0.5-2.5 mL (20-100 mg articaine HCl) - For nerve block: 0.5-3.4 mL (20-136 mg articaine HCl) - For oral surgery: 1.0-5.1 mL (40-204 mg articaine HCl) For most routine dental procedures, SEPTOCAINE containing epinephrine 1:200,000 is preferred. However, when more pronounced hemostasis or improved visualization of the surgical field are required, SEPTOCAINE containing epinephrine 1:100,000 may be used. Maximum recommended dosages: - Healthy adults: 7 mg/kg of articaine HCl and 0.0017mg/kg of epinephrine (equivalent to 0.175 mL/kg for either product presentation, articaine HCl and epinephrine 1:100,000 or 1:200,000) - Pediatric patients 4-16 years: 7 mg/kg of articaine HCl and 0.0017mg/kg of epinephrine (equivalent to 0.175 mL/kg for either product presentation, articaine HCL and epinephrine 1:100,000 or 1:200, 000)

Table 4. Relevant Product Information for Articaine and the Listed Drug (LD).		
Product Name	Articaine	Septocaine[h] (NDA 020971)
How Supplied	Low-density polyethylene, single-dose vial with a 0.4 mL fill. One card of 5 single-dose vials is packaged into a foil pouch, with 10 foil pouches in a carton. NDC (XXXXXXXXXX) Package of 10 foil pouches, equivalent to 50 single-patient-use vials.	Single dose glass cartridges, packaged in boxes of 50 cartridges in the following two strengths (less than a full cartridge or more than one cartridge may be used for an individual patient). Monoject Disposable Dental Injector available in cardboard boxes containing 30 disposable single-dose injectors, each containing a single 1.7 mL cartridge.
Storage	(b)(4)°C to 25°C ((b)(4)°F to 77°F), not to exceed the expiration date printed on the carton and pouch. Discard after use.	Controlled room temperature 25°C (77°F) with brief excursions permitted between 15° and 30°C (59°F-86°F) [see USP Controlled Room Temperature]. Protect from light. Do Not Freeze.
Container Closure	\\CDSESUB1\EVSPROD\nda218643\0001\m3\32-body-data\32p-drug-prod\articaine-ster-top-sol\32p7-cont-closure-sys\32p7-container-closure-system.pdf	Cartridge

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Articaine labels and labeling submitted by American Genomics, LLC.

- Prescribing Information received on January 24, 2025, available from:
  - Annotated version: \\CDSESUB1\EVSPROD\nda218643\0004\m1\us\114-labeling\draft\labeling\11413-prescribing-information-v0-6-redline.pdf
  - Clean version: \\CDSESUB1\EVSPROD\nda218643\0004\m1\us\114-labeling\draft\labeling\11413-prescribing-information-v0-6.docx
- Container label(s) received on February 4, 2025
- Carton labeling received on January 24, 2025
- Foil pouch labeling received on January 24, 2025

B.2 Container Label, Foil Pouch, and Carton Labeling Images

Container Label:

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX C. PREVIOUS DMEPA REVIEWS

On February 5, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, articaine, and 218643. Our search did not identify any previous reviews.

APPENDIX D. INFORMATION REQUEST (IR)

Response to Information Requests, received on February 4, 2025, available from \\CDSESUB1\EVSPROD\nda218643\0005\m1\us\12-cover-letters\cover-letter.pdf

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VALERIE S VAUGHAN
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Clinical Inspection Summary

Date	March 24, 2025
From	Roy Blay, Ph.D. Michele Fedowitz, M.D. Jenn Sellers, M.D., Ph.D. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	William Boyd, M.D., Deputy Division Director Rhea Lloyd, M.D., Clinical Team Leader Shilpa Rose, M.D., Reviewing M.O. Nick Connis, P.M. Division of Ophthalmology
NDA	218643
Applicant	American Genomics, LLC
Drug	Articaine Sterile Topical Ophthalmic Solution 8%
NME	No
Therapeutic Classification	Nerve impulse conduction inhibition by sodium channel block
Proposed Indication(s)	For ocular surface anesthesia prior to ocular procedures and/or intraocular injections.
Consultation Request Date	4 Dec 2024
Summary Goal Date	15 Jun 2025
Action Goal Date	15 Aug 2025
PDUFA Date	15 Aug 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Protocols AG-920-CS301 and AG-920-CS302 were submitted to the Agency in support of NDA 218643 for the use of Articaine Sterile Topical Ophthalmic Solution 8% for topical ocular use to provide local anesthesia prior to ocular procedures and/or intraocular injections. Drs. Wirta and Gonzalez were inspected in support of this NDA.

Based on the results of these inspections, Protocols AG-920-CS301 and AG-920-CS302 appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

The Applicant submitted this NDA to support the use of articaine for ocular surface anesthesia prior to ocular procedures and/or intraocular injections.

Inspections were requested of the following protocols in support of this application:

Protocol Numbers and Titles: **Protocol AG-920-CS301** and **Protocol AG-920-CS302** are both entitled, "A Randomized, Double-Masked, Vehicle-Controlled, Parallel Evaluation of the Local Anesthetic Effect of Articaine Sterile Topical Ophthalmic Solution"

Protocols AG-920-CS301 and AG-920-CS302

These protocols were designed similarly to assess the safety and efficacy of articaine as a local anesthetic for ocular surface anesthesia prior to ocular procedures and/or intraocular injections. Both studies shared the same efficacy objectives, treatment schedules, and subject qualification criteria. These protocols were Phase 3, randomized, placebo-controlled, double-masked, parallel design studies whose primary efficacy objectives were to evaluate the safety, efficacy, and tolerability of articaine as a local anesthetic.

Eligible subjects attended a Screening Visit, a treatment and anesthesia testing visit, and a follow-up visit (by telephone). Eligible subjects were randomized in a 1:1 ratio to a single dose of AG-920 or placebo into the study eye (two drops 30 seconds apart). Subjects underwent a conjunctival pinch and the resulting pain, if any, was assessed at specified time intervals.

The primary efficacy endpoint of the study was the proportion of subjects with no pain at 5 minutes.

For Protocol AG-920-CS301, a total of 120 subjects were planned for randomization at this single-site study at the site of Dr. Wirta. The study period was from 3-30 September 2020.

For protocol Ag-920-CS302, a total of 120 subjects were planned for randomization at this single-site study at the site of Dr. Gonzalez. The study period was from 30 March-10 May 2020.

1. **David L. Wirta, M.D.**
   Eye Research Foundation
   520 Superior Avenue, Suite 235
   Newport Beach, CA 92663

   Site: 01
   Protocol: AG-920-CS301
   Inspection Dates: 03-06 Mar 2025

   Dr. Wirta was inspected for the conduct of Protocol AG-920-CS301**.** This was the eighth inspection of Dr. Wirta. At this site, 120 subjects were screened, enrolled, and completed the study.

The study files of 70 subjects were reviewed**,** including the verification of the primary endpoint and the reporting of adverse events. Subject records reviewed included study eligibility, the informed consent forms for all 120 subjects, randomization, protocol deviations, and concomitant medications.

Study related documents reviewed included the Form 1572, IRB, sponsor, and monitor correspondence, training documentation, delegation logs, investigational product (IP) shipment, receipt, storage, and disposition records, electronic records, and financial disclosures.

The inspection compared the source documents with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

2. Victor H. Gonzalez, MD
Valley Retina Institute, PA
1309 E. Ridge Road
McAllen, TX 78503

Site: 02
Protocol: AG-920-CS302
Inspection Dates: 24-28 February 2025

Dr. Gonzalez was inspected for the conduct of Protocol AG-920-CS302. This was the second inspection of Dr. Gonzalez. At this site, 121 subjects were screened, 120 subjects were enrolled, and all 120 enrolled subjects completed the study.

The study files of all screened subjects were reviewed**,** including the verification of the primary efficacy endpoint and the reporting of adverse events. Subject records reviewed included study eligibility, informed consent, randomization, subject dosing, protocol deviations, discontinuations, and concomitant medications.

Study related documents reviewed included the Form 1572, IRB, sponsor, and monitor correspondence, training documentation, investigational product (IP) receipt, storage, accountability, and dispensation records, electronic records, and financial disclosures.

The inspection compared the source documents and case report forms (CRFs) with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
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DO/Medical Team Leader/Rhea Lloyd
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DO/Project Manager/Nick Connis
OSI/Office Director/David Burrow
OSI/Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
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OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

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