

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-114**

**CHEMISTRY REVIEW(S)**

**CMC Review of NDA 22-114**

**Zingo®  
(Lidocaine HCl H<sub>2</sub>O Powder Intradermal Injection System)**

**Anesiva, Inc.**

**William M. Adams  
OFFICE OF NEW DRUG QUALITY ASSESSEMENT  
DIVISION OF PREMARKETING ASSESSMENT AND  
MANUFACTURING SCIENCE (BRANCH V)  
FOR THE DIVISION OF ANESTHESIA, ANALGESIA and  
RHEUMATOLOGY PRODUCTS (HFD-170)**

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# Chemistry Review Data Sheet

1. NDA 22-114
2. REVIEW #1
3. REVIEW DATE: 08 Aug 2007
4. REVIEWER: William Adams
5. PREVIOUS DOCUMENTS: None
6. SUBMISSIONS BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
N-000	21 Nov 2006
N-004	13 Apr 2007
N-005	07 May 2007
N-008	22 Jun 2007
N-009	20 Jul 2007
BC*	14 Aug 2007

\*E-mail submission not yet in COMIS

7. NAME & ADDRESS OF APPLICANT:

Name:	Anesiva, Inc.
Address:	650 Gateway Boulevard South San Francisco, CA 94080
Representative:	Carol Zoltowski, VMD Senior Director, Regulatory Affairs
Telephone:	(650) 246-6844

8. DRUG PRODUCT NAME/CODE/TYPE:

- (a) Proprietary Name: Zingo
- (b) Non-Proprietary Name: Lidocaine Powder Intradermal Injection System
- (c) Code Name/# (ONDC only): ALGRX 3268 \*
- (d) Chem. Type/Submission Priority (ONDC only): 1S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2). RLDs: Lidoderm (NDA 20-612), and Synera (NDA 21-623)

10. PHARMACOLOGICAL CATEGORY: local anesthetic

11. DOSAGE FORM: Powder

12. STRENGTH/POTENCY: 0.50 mg/dose

13. ROUTE OF ADMINISTRATION: Intradermal

14. Rx/OTC DISPENSED: Rx

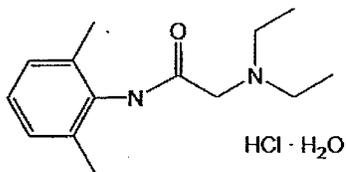
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

\_\_\_\_\_ SPOTS product – Form Completed

XX Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Lidocaine HCl, USP



Molecular Formula C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O · HCl · H<sub>2</sub>O

Molecular Weight 288.8 Da

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
_____	II	┌	┌ └	1	Adequate	05/25/07	API starting material
_____	III		┌	1	Adequate	pending	DP component
_____	III	└	└	1	Adequate	06/14/07	Device component

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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Chemistry Review Data Sheet

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")
- <sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	54,740	ND5 devices

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted. Approval	07/30/07	Y. Kim
EES	Acceptable	06/12/07	OC
Pharm/Tox	Not consulted. Approval	07/10/07	G. Bonds
Biopharm	Not consulted. Approval	07/24/07	S. Nallani
Clinical	Approval	07/31/07	H. Josefberg
Methods Validation	Complete and adequate MV studies are provided. No need for requesting method validation studies at DPA as the methods are conventional and do not meet any of the seven criteria for method validation requests.	---	---
ODS/DMETs	Acceptable	08/03/07	L. Holmes
DDMAC	Comments	03/23/07	M. Safaik
EA	Acceptable	this review	M. Adams
CDRH, Microbiology	Approval	07/30/07	P. Soprey, CDRH

**19. ORDER OF REVIEW: N/A**

**Appears This Way  
On Original**

# The Chemistry Review for NDA 22-114

## The Executive Summary

### I. RECOMMENDATIONS

#### A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

All CMC approvability issues have been resolved adequately. In an amendment dated August 14, 2007, the applicant addressed additional questions pertaining to the proposed comparability protocols. The office of compliance deemed the facilities acceptable for cGMP compliance. Therefore, the application is recommended for approval from CMC viewpoint. The following comment should be included in the action letter.

“Revise the sampling plan for the device actuation testing (Method ASV-009) to provide for an AQL of — for defect rate and specify test sample size based on the proposed commercial batch size.”

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#### B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS &/or RISK MANAGEMENT STEPS, if Approvable

None

### II. SUMMARY OF CHEMISTRY ASSESSMENTS

#### A. DESCRIPTION OF THE DRUG PRODUCT(S) & DRUG SUBSTANCE(S)

This is an application for a Drug-Device Combination Product. The Combination Product is 0.5 mg Lidocaine HCl H<sub>2</sub>O (LHM) Sized Powder (40 μm nominal particle size) contained in a cassette composed of matching male/female [redacted] film within a device. This device is a sterile, multi-part needle-free drug delivery system which presents as a tube with a cone at one end and an actuator button at the other. When actuated by the thumb, the neck of a helium gas capsule is broken to release a burst of gas which is directed down the tube through the cassette to burst the [redacted] film releasing the LHM powder which is injected into the dermal layer of the skin. Drug injected in this manner produces a roughly circular area of anesthetized skin. The product is intended for patients who are sensitive to the pain resulting from venipuncture or intravenous cannulation.

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The Drug Product [LHM Filled Cassette] is assembled by a contractor [redacted] using LHM Sized Powder obtained from a contractor [redacted] matching male/female [redacted] bodies provided by the device manufacturer (The Tech Group) and [redacted] film obtained from a commercial supplier. All manufacturing and control facilities meet cGMP requirements. The cassette is to be assembled by either a manual or automated process under humidity controlled conditions. Manufacturing processes, their in process controls and environmental controls are described in detail and justified by the developmental and stability studies. Cassettes are bulk packaged and shipped to the device manufacture. Release specifications have been established to address identity, content uniformity, assay and moisture content; impurities and degradants are addressed on the sterile device. The analytical methods are described in detail and validated. The criteria are justified by the developmental studies and stability data. Stability studies performed under ICH conditions are adequate to support the proposed storage statement of [redacted] at controlled room temperature.

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Executive Summary Section

components; the information has been requested. The analytical methods are identified and the criteria are justified by the developmental studies. Specifications for cassette acceptance, release of non-sterile LHM product and release of Sterile LHM Product are established to address identity, purity, degradants, device function, emitted dose, foreign particulates, sterility assurance and bacterial endotoxins. The analytical methods are described in detail and are validated. The criteria are justified by developmental and stability studies. Sterility assurance is based on [redacted] and an in-process test for pouch integrity. The stability studies performed under ICH conditions are adequate to justify the proposed expiry period and label storage statement - 24 months at controlled room temperature.

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The Drug Substance is Lidocaine HCl H<sub>2</sub>O Sized Powder which has been manufactured by [redacted]

[redacted] Lidocaine HCl, USP is obtained from a contract supplier [redacted] and sieved by another contractor [redacted]. All manufacturing and control facilities meet cGMP requirements. The starting material supplier has provided adequate characterization and proof of structure information in their type II DMF [redacted]. The acceptance specification for starting material adequately addresses identity, assay, and inorganic and organic impurities. The drug substance (LHM Sized Powder) specifications adequately address identity and critical physical attributes. The lots are accepted based on the values for assay and impurities from the supplier's certificate of analysis. The analytical methods are described in detail and are validated. The criteria are justified by the development studies, historical batch analysis data and the stability information. Reference standards for drug substance and specified impurities are identified and characterized. Studies performed at ICH conditions are adequate to support the proposed label storage statement of 24 months at controlled room temperature.

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The drug product and device manufacturers have justified a claimed categorical exclusion under 21 CFR 25.34(c) in that the proposed product will not significantly increase the environment to exposure to drug or the materials used in the construction of the device.

The applicant has submitted draft package insert labeling, and labels for the device, pouch and carton. The labels are adequate with respect to the CMC information except for the established name which does not indicate the dose as being expressed as the HCl salt. The firm is expected to respond to additional labeling comments.

The application includes three comparability protocols. The first is for manufacturing scale-up and a facility change within the contiguous area of the firm for LHM Filled Cassettes, which is to be filed as a CBE-30 supplemental application. The second is for manufacturing scale-up for non-sterile device, which is to be filed as a CBE-30 supplemental application. The third is for justifying a new supplier of [redacted] film (the NDA source will no longer be available) which was proposed to be filed in an Annual Report. However, owing to the critical role played by the [redacted] film in the drug delivery, the firm was asked to submit this change in a CBE-30 supplement. The protocols describe the proposed changes in detail, and propose to submit adequate data necessary to justify the changes. With the CMC amendment dated 08/20/2007, the protocols are now considered to be adequate to implement future CMC changes.

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**B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED**

The device is to be grasped with a fist with the hollow end placed firmly against the site to be anesthetized. When the actuator button is pushed with the thumb, lidocaine HCl H<sub>2</sub>O sized powder is injected into the skin to form a roughly round anesthetized spot of skin. The patient may then receive venipuncture or intravenous cannulation without pain.

**C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION**

All CMC approvability issues have been resolved adequately. In an amendment dated August 14, 2007, the applicant addressed additional questions pertaining to the proposed comparability protocols. The office of

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compliance deemed the facilities acceptable for cGMP compliance. Therefore, the application is recommended for approval from CMC viewpoint.

**III. ADMINSTRATIVE**

**A. REVIEWER'S SIGNATURE**

\_\_\_\_\_  
William M. Adams

**B. ENDORSEMENT BLOCK**

M.Adams/ONDQA  
R.Harapanhalli/DPMA III/Chief Branch V  
K.Stiller/PM/ONDQA  
G.Smith/DAARP (HFD-170)

**C. CC BLOCK**

Rik Lostritto/ONDQA/Dir DPMA III

114 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Mike Adams  
8/14/2007 11:41:57 AM  
CHEMIST

Ravi Harapanhalli  
8/14/2007 11:52:24 AM  
CHEMIST

A CMC comment to be included in the letter.



Milestone Date: 04-JAN-07  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : [ ] [ ] FEI : [ ] [ ]

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DMF No: [ ] AADA:

Responsibilities: [ ] [ ]

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Profile : [ ] OAI Status: NONE

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Last Milestone: OC RECOMMENDATION

Milestone Date: 28-DEC-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : [ ] [ ] FEI : [ ] [ ]

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DMF No: [ ] AADA:



Profile : —

OAI Status: NONE

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Last Milestone: OC RECOMMENDATION

Milestone Date: 12-JUN-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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