

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-114

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



Anesiva, Inc.
Sterile LHM Product (Lidocaine 0.5mg Needlefree Disposable System)

b(4)

Statement pursuant to 21 USC Sec 505(b)(2)(B)

RE: U.S. Patent Nos. 5,411,738; 5,589,180; 5,601,838; and 5,709,869

Anesiva, Inc. states that its proposed label for Anesiva's product does not include any indications that are covered by the following U.S. Patents:

U.S. Patent No. 5,411,738 that expires on May 2, 2012

U.S. Patent No. 5,589,180 that expires on March 17, 2009

U.S. Patent No. 5,601,838 that expires on May 2, 2012; and

U.S. Patent No. 5,709,869 that expires on March 17, 2009

ANESIVA, INC.

By:

John P. McLaughlin
Chief Executive Officer and Director
Anesiva, Inc.
650 Gateway Boulevard
South San Francisco, California 94080

• HEADQUARTERS:

650 GATEWAY BOULEVARD
SOUTH SAN FRANCISCO, CA 94080
PHONE (650) 624-9600
FAX (650) 624-7540
WWW.ANESIVA.COM

500 PLAZA DRIVE
SECAUCUS, NJ 07094
PHONE (201) 325-6900
FAX (201) 325-6909

161 WASHINGTON STREET, SUITE 990
CONSHOHOCKEN, PA 19428
PHONE (610) 828-3401
FAX (610) 828-3697

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22114

NAME OF APPLICANT / NDA HOLDER

ANESIVA, INC.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
STERILE LHM PRODUCT

ACTIVE INGREDIENT(S)
LIDOCAINE

STRENGTH(S)
0.5MG

DOSAGE FORM
NEEDLE-FREE INJECTION

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,899,880

b. Issue Date of Patent
5/4/1999

c. Expiration Date of Patent
5/4/2016

d. Name of Patent Owner
POWDERJECT RESEARCH LIMITED

Address (of Patent Owner)
PARK GATE, 25 MILTON PARK

City/State
OXFORD, OX14 4SH

ZIP Code
ENGLAND

FAX Number (if available)

Telephone Number
44 1865 501500

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2. Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Patricia B...
Vice President & General Counsel

10/2/06

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
ANESIVA, INC.

Address
650 GATEWAY BOULEVARD

City/State
SOUTH SAN FRANCISCO, CALIFORNIA

ZIP Code
94080

Telephone Number
(650) 624-9600

FAX Number (if available)
(650) 924-7540

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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**PATENT INFORMATION SUBMITTED WITH THE
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*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22114

NAME OF APPLICANT / NDA HOLDER

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The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

STERILE LHM PRODUCT

ACTIVE INGREDIENT(S)

LIDOCAINE

STRENGTH(S)

0.5MG

DOSAGE FORM

NEEDLE-FREE INJECTION

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1. GENERAL

a. United States Patent Number
6,004,286

b. Issue Date of Patent
12/21/1999

c. Expiration Date of Patent
3/17/2017

d. Name of Patent Owner
POWDERJECT RESEARCH LIMITED

Address (of Patent Owner)
PARK GATE, 25 MILTON PARK

City/State
OXFORD, OX14 4SH

ZIP Code
ENGLAND

FAX Number (if available)

Telephone Number
44 1865 501500

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed

Pat a B...
 Vice President and General Counsel

10/2/06

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NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
 ANESIVA, INC.

Address
 650 GATEWAY BOULEVARD

City/State
 SOUTH SAN FRANCISCO, CALIFORNIA

ZIP Code
 94080

Telephone Number
 (650) 624-9600

FAX Number (if available)
 (650) 924-7540

E-Mail Address (if available)

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**PATENT INFORMATION SUBMITTED WITH THE
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*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22114

NAME OF APPLICANT / NDA HOLDER

ANESIVA, INC.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
STERILE LHM PRODUCT

ACTIVE INGREDIENT(S)
LIDOCAINE

STRENGTH(S)
0.5MG

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1. GENERAL

a. United States Patent Number
6,881,200

b. Issue Date of Patent
4/19/2005

c. Expiration Date of Patent
6/11/2016

d. Name of Patent Owner
POWDERJECT RESEARCH LIMITED

Address (of Patent Owner)
PARK GATE, 25 MILTON PARK

City/State
OXFORD, OX14 4SH

ZIP Code
ENGLAND

FAX Number (if available)

Telephone Number
44 1865 501500

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

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2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

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Date Signed

10/2/06

Vice President and General Counsel

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
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Address
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5/7/07

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
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*For Each Patent That Claims a Drug Substance
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NDA NUMBER

22-114

NAME OF APPLICANT / NDA HOLDER

ANESIVA, INC.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Zingo

ACTIVE INGREDIENT(S)

Lidocaine Hydrochloride Monohydrate

STRENGTH(S)

0.5mg

DOSAGE FORM

NEEDLE-FREE DISPOSABLE INJECTION

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1. GENERAL

a. United States Patent Number

5,630,796

b. Issue Date of Patent

5/20/1997

c. Expiration Date of Patent

5/20/2014

d. Name of Patent Owner
OXFORD BIOSCIENCES

Address (of Patent Owner)

THE MAGDALEN CENTRE
OXFORD SCIENCES PARK

City/State

OXFORD OX1 4GA

ZIP Code

ENGLAND

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

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2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number (as listed in the patent) 1-5 and 9-13	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Zingo is indicated for the use on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input checked="" type="checkbox"/> Yes
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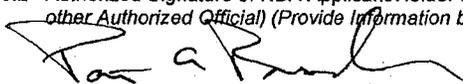
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



4/27/07

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
ANESIVA, INC.

Address
650 GATEWAY BOULEVARD

City/State
SOUTH SAN FRANCISCO, CALIFORNIA

ZIP Code
94080

Telephone Number
(650) 624-9600

FAX Number (if available)
(650) 924-7540

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



07 May 2007

Bob A. Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705

Subject: NDA No. 22-114
Lidocaine Powder Delivery System (Formerly Sterile LHM Product)
Amendment to a Pending Application:
Patent Certification - Notice of Certification
Sequence No. 0005

Dear Dr. Rappaport,

Reference is made to the original Investigational New Drug (IND) application for ALGRX 3268 (Dermal PowderJect Lidocaine HCl Delivery System) to provide local analgesia prior to venipuncture and intravenous cannulation, submitted to the Agency on 10 December 1997. In addition, reference is made to the original New Drug Application (NDA) submitted to the Agency on 21 November 2006. Please note that the established name of the Final Product is now designated as the Lidocaine Powder Delivery System.

• HEADQUARTERS:

650 GATEWAY BOULEVARD
SOUTH SAN FRANCISCO, CA 94080
PHONE (650) 624-9600
FAX (650) 624-7540
WWW.ANESIVA.COM

500 PLAZA DRIVE
SECAUCUS, NJ 07094
PHONE (201) 325-6900
FAX (201) 325-6909

161 WASHINGTON STREET, SUITE 990
CONSHOHOCKEN, PA 19428
PHONE (610) 828-3401
FAX (610) 828-3697

PAGE 1

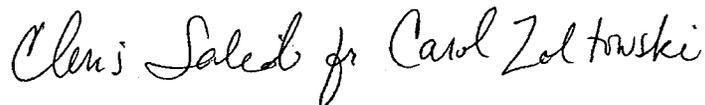
The purpose of this submission is to provide the following documents under Module 1, section 1.3.5.2 Patent Certification:

- Statements of certification as required by CFR 314.52 (b) that notices of certification of invalidity or non-infringement of a patent have been sent to each person identified under CFR 314.52 (a)
- Documentation of receipt of notice by each person provided the notice as required by CFR 314.52 (e).

In addition, patent information (Form FDA 3542a) for Oxford Biosciences is being provided. Oxford Biosciences, a subsidiary of PowderJect Technologies, Inc., was acquired by AlgoRx Pharmaceuticals, Inc. in 2002. In 2005, AlgoRx Pharmaceuticals, Inc. merged with Corgentech, Inc. to become Corgentech, Inc. In 2006, Corgentech, Inc. changed its name to Anesiva, Inc.

If you have any questions or comments regarding this submission, please contact Carol Zoltowski, V.M.D. at (650) 246-6825.

Best Regards,



Carol Zoltowski, V.M.D.
Senior Director and Head of Regulatory Affairs
Anesiva, Inc.

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SOUTH SAN FRANCISCO, CA 94080
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PARAGRAPH IV CERTIFICATION

Anesiva, Inc. certifies that, to the best of its knowledge, U.S. Patent No. 5,658,583; U.S. Patent No. 5,919,479; U.S. Patent No. 6,306,431; U.S. Patent No. 6,465,006; U.S. Patent No. 6,546,281; and U.S. Patent No. 6,780,426 will not be infringed by the manufacture, use, or sale of Anesiva, Inc.'s Sterile LHM Product (Lidocaine 0.5mg Needlefree Disposable System) for which this new drug application (NDA) No. 22114 is submitted, or in the alternative, that U.S. Patent No. 5,658,583; U.S. Patent No. 5,919,479; U.S. Patent No. 6,306,431; U.S. Patent No. 6,465,006; U.S. Patent No. 6,546,281; and U.S. Patent No. 6,780,426 are invalid and/or unenforceable.

As required by Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and 21 C.F.R. §§ 314.50 and 314.52, Anesiva, Inc. hereby states that this NDA is sufficiently complete to permit substantive review and that Anesiva, Inc. will give notice as required by 21 U.S.C. 355(b) and 21 CFR § 314.52 to Endo Pharmaceuticals, the NDA holder for Synera 70-70 Topical Patch, and to Zars Pharma, the owner of U.S. Patent No. 5,658,583; U.S. Patent No. 5,919,479; U.S. Patent No. 6,306,431; U.S. Patent No. 6,465,006; U.S. Patent No. 6,546,281; and U.S. Patent No. 6,780,426.

The notices will be sent by registered or certified mail, return receipt requested, and meet the requirements of 21 CFR § 314.52(a, c).

Concurrently with sending the notices to ENDO PHARMACEUTICALS, and ZARS PHARMA, Anesiva, Inc. will, as required by 21 CFR § 314.52(b), amend its NDA to include a certification that the notice has been provided to each person identified under 21 CFR § 314.52(a), and that the notices met the content requirements specified in 21 CFR § 314.52(c).

ANESIVA, INC.

By

John P. McLaughlin
Chief Executive Officer and Director
Anesiva, Inc.
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South San Francisco, California 94080

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PARAGRAPH IV CERTIFICATION

Anesiva, Inc. certifies that, to the best of its knowledge, U.S. Patent No. 5,411,738; U.S. Patent No. 5,589,180; U.S. Patent No. 5,601,838; U.S. Patent No. 5,790,869 and U.S. Patent No. 5,827,529 will not be infringed by the manufacture, use, or sale of Anesiva, Inc.'s Sterile LHM Product (Lidocaine [™] 0.5mg Needlefree Disposable System) for which this new drug application (NDA) No. 22114 is submitted, or in the alternative, that U.S. Patent No. 5,411,738; U.S. Patent No. 5,589,180; U.S. Patent No. 5,601,838; U.S. Patent No. 5,790,869 and U.S. Patent No. 5,827,529 are invalid and/or unenforceable.

b(4)

As required by Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and 21 C.F.R. §§ 314.50 and 314.52, Anesiva, Inc. hereby states that this NDA is sufficiently complete to permit substantive review and that Anesiva, Inc. will give notice as required by 21 U.S.C. 355(b) and 21 CFR § 314.52 to Teikoku Pharma USA, Inc., the NDA holder for Lidoderm 5% Topical Patch., and to, Hind Health Care Inc., the owner of U.S. Patent No. 5,411,738; U.S. Patent No. 5,589,180; U.S. Patent No. 5,601,838; U.S. Patent No. 5,790,869 and Teikoku Seiyaku Kabushiki Kaisha, the owner of U.S. Patent No. 5,827,529.

The notices will be sent by registered or certified mail, return receipt requested, and meet the requirements of 21 CFR § 314.52(a, c).

Concurrently with sending the notices to TEIKOKU PHARMA USA, INC., HIND HEALTH CARE, INC. and TEIKOKU SEIYAKU KABUSHIKI KAISHA, Anesiva, Inc. will, as required by 21 CFR § 314.52(b), amend its NDA to include a certification that the notice has been provided to each person identified under 21 CFR § 314.52(a), and that the notices met the content requirements specified in 21 CFR § 314.52(c).

ANESIVA, INC.

By:

John P. McLaughlin
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South San Francisco, California 94080

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650 GATEWAY BOULEVARD
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5/7/07

PARAGRAPH IV CERTIFICATION

Anesiva, Inc. certifies that, to the best of its knowledge, U.S. Patent No. 5,411,738; U.S. Patent No. 5,589,180; U.S. Patent No. 5,601,838; U.S. Patent No. 5,790,869 and U.S. Patent No. 5,827,529 will not be infringed by the manufacture, use, or sale of Anesiva, Inc.'s Zingo™, Dermal PowderJect Lidocaine HCl Delivery System/Sterile LHM Product, topical powder, 0.5mg, for which this New Drug Application (NDA) No. 22-114 was submitted on November 21, 2006, or in the alternative, that U.S. Patent No. 5,411,738; U.S. Patent No. 5,589,180; U.S. Patent No. 5,601,838; U.S. Patent No. 5,790,869 and U.S. Patent No. 5,827,529 are invalid and/or unenforceable.

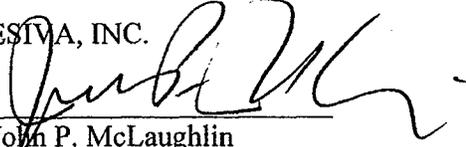
As required by Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and 21 C.F.R. §§ 314.50 and 314.52, Anesiva, Inc. hereby states that this NDA is sufficiently complete to permit substantive review and that in accordance with 21 C.F.R. §§ 314.52(a) and (b), Anesiva, Inc. sent a "Patent Certification Under 21 U.S.C. §355 and Notice of Certification of Invalidity and Non-Infringement of Patent under 21 U.S.C. §355" (hereinafter "the Notice") on April 4, 2007, to the following:

- A. TEIKOKU PHARMA USA as NDA holder of Lidoderm® Patch (Lidocaine patch 5% w/w).
- B. ENDO PHARMACEUTICALS INCORPORATED as owner of listed patent nos. U.S. 5,411,738; 5,589,180; 5,601,838; and 5,709,868;
- C. HIND HEALTH CARE, INCORPORATED as owner of listed patent nos. U.S. 5,411,738; 5,589,180; 5,601,838; and 5,709,868;
- D. TEIKOKU SEIYAKU KABUSHIKI KAISHA as owner of listed patent no. U.S. 5,827,529; and
- E. BIRCH, STEWART, KOLASCH & BIRCH as correspondent of record for U.S. Patent No. 5,827,529.

The Notices meet the requirements under 21 C.F.R. § 314.52(c). Copies of the Notices are attached as Exhibit A, copies of the United States Postal Service receipts of mailing of the Notices to ENDO PHARMACEUTICALS INCORPORATED; HIND HEALTH CARE, INCORPORATED and TEIKOKU PHARMA USA showing that the Notices were sent U.S. registered mail, return receipt requested on April 4, 2007 are attached as Exhibit B, and a copy of the Federal Express Delivery Confirmation receipt showing that Notice was sent On April 4, 2007, to TEIKOKU SEIYAKU KABUSHIKI KAISHA is attached as Exhibit C.

ANESIVA, INC.

By:


John P. McLaughlin
Chief Executive Officer and Director
Anesiva, Inc.
650 Gateway Boulevard
South San Francisco, California 94080

PARAGRAPH IV CERTIFICATION

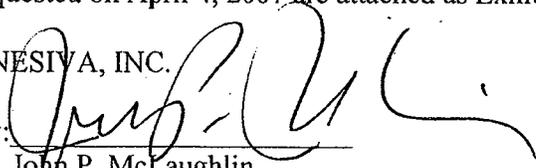
Anesiva, Inc. certifies that, to the best of its knowledge, U.S. Patent No. 5,658,583; U.S. Patent No. 5,919,479; U.S. Patent No. 6,306,431; U.S. Patent No. 6,465,006; U.S. Patent No. 6,546,281; and U.S. Patent No. 6,780,426 will not be infringed by the manufacture, use, or sale of Anesiva, Inc.'s Zingo™, Dermal PowderJect Lidocaine HCl Delivery System/Sterile LHM Product, topical powder, 0.5mg, for which this New Drug Application (NDA) No. 22-114 was submitted on November 21, 2006, or in the alternative, that U.S. Patent No. 5,658,583; U.S. Patent No. 5,919,479; U.S. Patent No. 6,306,431; U.S. Patent No. 6,465,006; U.S. Patent No. 6,546,281; and U.S. Patent No. 6,780,426 are invalid and/or unenforceable.

As required by Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and 21 C.F.R. §§ 314.50 and 314.52, Anesiva, Inc. hereby states that this NDA is sufficiently complete to permit substantive review and that in accordance with 21 C.F.R. §§ 314.52(a) and (b), Anesiva, Inc. sent a "Patent Certification Under 21 U.S.C. §355 and a Notice of Certification of Invalidity and Non-Infringement of Patent under 21 U.S.C. §355" (hereinafter "the Notice") on April 4, 2007 to the following:

- A. ENDO PHARMACEUTICALS INCORPORATED as NDA holder of Synera™ Patch (Lidocaine 70mg/Tetracaine 70mg topical patch);
- B. ZARS PHARMA as owner of listed patent numbers U.S. 5,658,583; 5,919,479; 6,306,431; 6,465,006; 6,546,281 and 6,780,426;
- C. THORPE NORTH & WESTERN, LLP as Attorney of record for U.S. Patent Nos. 5,658,583 and 6,306,431; and
- D. KIRTON AND McCONKIE as Attorney of record for U.S. Patent Nos. 5,919,479; 6,465,006; 6,546,281 and 6,780,426.

The Notices meet the content requirements under 21 C.F.R. § 314.52(c). Copies of the Notices are attached as Exhibit A, and copies of the United States Postal Service receipts of mailing of the Notices to ZARS PHARMA; ENDO PHARMACEUTICALS INCORPORATED; THORPE NORTH & WESTERN, LLP; and KIRTON AND McCONKIE showing that the Notices were sent U.S. registered mail, return receipt requested on April 4, 2007, are attached as Exhibit B.

ANESIVA, INC.

By: 

John P. McLaughlin
Chief Executive Officer and Director
Anesiva, Inc.
650 Gateway Boulevard
South San Francisco, California 94080

~~EXHIBIT A~~



6/22/07

June 15, 2007

Gerri Smith
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: Anesiva New Drug Application (NDA # 22-114)

Gerri:

We have enclosed herewith two amended Paragraph IV Certifications for submission to the FDA for the above-referenced NDA filing.

The first updated Paragraph IV Certification is in reference to U.S. Patent No. 5,411,738; U.S. Patent No. 5,589,180; U.S. Patent No. 5,601,838; U.S. Patent No. 5,709,869 and U.S. Patent No. 5,827,529 (the Lidoderm[®] patents). This amended Paragraph IV Certification is being submitted upon your request to clarify the typographical error with regard to U.S. Patent No. 5,709,869. This Paragraph IV Certification has also been amended to reflect the fact that Anesiva is providing the FDA with copies of the Domestic Return Receipt Postcards (or other similar evidence of the date Notice was received) as proof of delivery of the Notice Letters in accordance with 21 C.F.R. § 314.52(e). Accordingly, we are submitting herewith:

1. Copies of the United States Postal Service Domestic Return Receipt postcards to ENDO PHARMACEUTICALS INCORPORATED; TEIKOKU PHARMA USA; and BIRCH, STEWART, KOLASCH AND BIRCH showing that the Notices were received by registered mail on April 6, 2007 and April 9, 2007 (Exhibit B);
2. Copies of the Federal Express Delivery Confirmation receipt showing that Notice was received on April 9, 2007 by TEIKOKU SEIYAKU KABUSHIKI KAISHA (Exhibit C); and
3. Copies of the United States Postal Service receipt of mailing of the Notices to HIND HEALTH CARE, INCORPORATED together with copies of the corresponding United States Postal Service "Track and Confirm" results as proof that the Notice Letters were delivered on April 10, 2007 (Exhibit D).

• HEADQUARTERS:

650 GATEWAY BOULEVARD
SOUTH SAN FRANCISCO, CA 94080
PHONE (650) 624-9600
FAX (650) 624-7540
WWW.ANESIVA.COM

500 PLAZA DRIVE
SECAUCUS, NJ 07094
PHONE (201) 325-6900
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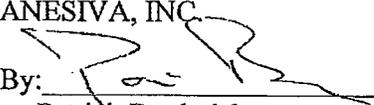
The second Paragraph IV Certification is in reference to U.S. Patent Nos. 5,658,583; 5,919,479; 6,306,431; 6,465,006; 6,546,281 and 6,780,426 (Synera™ patents). This amended Paragraph IV Certification is being submitted to reflect the fact that Anesiva is providing the FDA with copies of the Domestic Return Receipt Postcards (or other similar evidence of the date Notice was received) as proof of delivery of the Notice Letters in accordance with 21 C.F.R. § 314.52(e). Accordingly, we are submitting herewith:

1. Copies of the United States Postal Service Domestic Return Receipt postcards to ENDO PHARMACEUTICALS INCORPORATED; and THORPE NORTH & WESTERN, LLP showing that the Notices were received by registered mail on April 9, 2007 (Exhibit B), and
2. Copies of the United States Postal Service Domestic Return Receipt postcards to ZARS PHARMA and KIRTON AND MCCONKIE together with copies of the corresponding United States Postal Service "Track and Confirm" results as proof that the Notice Letters were delivered on April 9, 2007 (Exhibit C).

We have not attached copies of the Notice Letters referred to as Appendix A in both amended Paragraph IV Certifications, as copies of the Notice Letters were submitted with the previous amended Paragraph IV Certifications.

Should you require Anesiva to provide any additional information, please do not hesitate to contact us.

ANESIVA, INC

By: 

Patrick Broderick

Vice President, General Counsel and Corporate Secretary

Anesiva, Inc.

650 Gateway Boulevard

South San Francisco, California 94080

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650 GATEWAY BOULEVARD
SOUTH SAN FRANCISCO, CA 94080
PHONE (650) 624-9600
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SECAUCUS, NJ 07094
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161 WASHINGTON STREET, SUITE 990
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WWW.ANESIVA.COM

PARAGRAPH IV CERTIFICATION

Anesiva, Inc. certifies that, to the best of its knowledge, U.S. Patent No. 5,411,738; U.S. Patent No. 5,589,180; U.S. Patent No. 5,601,838; U.S. Patent No. 5,709,869 and U.S. Patent No. 5,827,529 will not be infringed by the manufacture, use, or sale of Anesiva, Inc.'s Zingo™, Dermal PowderJect Lidocaine HCl Delivery System/Sterile LHM Product, topical powder, 0.5mg, for which this New Drug Application (NDA) No. 22-114 was submitted on November 21, 2006, or in the alternative, that U.S. Patent No. 5,411,738; U.S. Patent No. 5,589,180; U.S. Patent No. 5,601,838; U.S. Patent No. 5,709,869 and U.S. Patent No. 5,827,529 are invalid and/or unenforceable.

As required by Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and 21 C.F.R. §§ 314.50 and 314.52, Anesiva, Inc. hereby states that this NDA is sufficiently complete to permit substantive review and that in accordance with 21 C.F.R. §§ 314.52(a) and (b), Anesiva, Inc. sent a "Patent Certification Under 21 U.S.C. §355 and Notice of Certification of Invalidity and Non-Infringement of Patent under 21 U.S.C. §355" (hereinafter "the Notice") on April 4, 2007, to the following:

- A. TEIKOKU PHARMA USA as NDA holder of Lidoderm® Patch (Lidocaine patch 5% w/w).
- B. ENDO PHARMACEUTICALS INCORPORATED as owner of listed patent nos. U.S. 5,411,738; 5,589,180; 5,601,838; and 5,709,869;
- C. HIND HEALTH CARE, INCORPORATED as owner of listed patent nos. U.S. 5,411,738; 5,589,180; 5,601,838; and 5,709,869;
- D. TEIKOKU SEIYAKU KABUSHIKI KAISHA as owner of listed patent no. U.S. 5,827,529; and
- E. BIRCH, STEWART, KOLASCH & BIRCH as correspondent of record for U.S. Patent No. 5,827,529.

The Notices meet the requirements under 21 C.F.R. § 314.52(c). Copies of the Notices are attached as Exhibit A, copies of the United States Postal Service Domestic Return Receipt postcards to ENDO PHARMACEUTICALS INCORPORATED; TEIKOKU PHARMA USA; and BIRCH, STEWART, KOLASCH AND BIRCH showing that the Notices were received by registered mail on April 6, 2007 and April 9, 2007 are attached as Exhibit B, a copy of the Federal Express Delivery Confirmation receipt showing that Notice was received on April 9, 2007 by TEIKOKU SEIYAKU KABUSHIKI KAISHA is attached as Exhibit C, copies of the United States Postal Service receipt of mailing of the Notices to HIND HEALTH CARE, INCORPORATED together with copies of the corresponding United States Postal Service "Track and Confirm" results as proof that the Notice Letters were delivered on April 10, 2007 are attached as Exhibit D.

ANESIVA, INC.

By: 

Patrick Broderick
Vice President, General Counsel and Corporate Secretary
Anesiva, Inc.
650 Gateway Boulevard
South San Francisco, California 94080

PARAGRAPH IV CERTIFICATION

Anesiva, Inc. certifies that, to the best of its knowledge, U.S. Patent No. 5,658,583; U.S. Patent No. 5,919,479; U.S. Patent No. 6,306,431; U.S. Patent No. 6,465,006; U.S. Patent No. 6,546,281; and U.S. Patent No. 6,780,426 will not be infringed by the manufacture, use, or sale of Anesiva, Inc.'s Zingo™, Dermal PowderJect Lidocaine HCl Delivery System/Sterile LHM Product, topical powder, 0.5mg, for which this New Drug Application (NDA) No. 22-114 was submitted on November 21, 2006, or in the alternative, that U.S. Patent No. 5,658,583; U.S. Patent No. 5,919,479; U.S. Patent No. 6,306,431; U.S. Patent No. 6,465,006; U.S. Patent No. 6,546,281; and U.S. Patent No. 6,780,426 are invalid and/or unenforceable.

As required by Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and 21 C.F.R. §§ 314.50 and 314.52, Anesiva, Inc. hereby states that this NDA is sufficiently complete to permit substantive review and that in accordance with 21 C.F.R. §§ 314.52(a) and (b), Anesiva, Inc. sent a "Patent Certification Under 21 U.S.C. §355 and a Notice of Certification of Invalidity and Non-Infringement of Patent under 21 U.S.C. §355" (hereinafter "the Notice") on April 4, 2007 to the following:

- A. ENDO PHARMACEUTICALS INCORPORATED as NDA holder of Synera™ Patch (Lidocaine 70mg/Tetracaine 70mg topical patch);
- B. ZARS PHARMA as owner of listed patent numbers U.S. 5,658,583; 5,919,479; 6,306,431; 6,465,006; 6,546,281 and 6,780,426;
- C. THORPE NORTH & WESTERN, LLP as Attorney of record for U.S. Patent Nos. 5,658,583 and 6,306,431; and
- D. KIRTON AND McCONKIE as Attorney of record for U.S. Patent Nos. 5,919,479; 6,465,006; 6,546,281 and 6,780,426.

The Notices meet the content requirements under 21 C.F.R. § 314.52(c). Copies of the Notices are attached as Exhibit A, and copies of the United States Postal Service Domestic Return Receipt postcards to ENDO PHARMACEUTICALS INCORPORATED; and THORPE NORTH & WESTERN, LLP showing that the Notices were received by registered mail on April 9, 2007 are attached as Exhibit B, copies of the United States Postal Service Domestic Return Receipt postcards to ZARS PHARMA and KIRTON AND MCCONKIE together with copies of the corresponding United States Postal Service "Track and Confirm" results as proof that the Notice Letters were delivered on April 9, 2007 are attached as Exhibit C.

ANESIVA, INC.

By: 

Patrick Broderick

Vice President, General Counsel and Corporate Secretary

Anesiva, Inc.

650 Gateway Boulevard

South San Francisco, California 94080

EXCLUSIVITY SUMMARY

NDA # 22-114

SUPPL #

HFD # 170

Trade Name Zingo

Generic Name lidocaine hydrochloride monohydrate powder intradermal injection system

Applicant Name Anesiva, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

There are numerous approved lidocaine-containing drug products. Those listed below had unexpired exclusivity at the time of submission of this application.

NDA# 21-451 Dentsply/Oraqix periodontal gel/with prilocaine/3-yr NDF exclusivity expired 19-Dec-06

NDA# 21-504 Vyteris/Lidosite topical patch/with epinephrine/3-yr NP exclusivity expired 04-May-07

NDA# 21-486 EMPI/topical solution/with epinephrine/3-yr NP exclusivity expires 26-Oct-07

NDA# 21-623 Synera/topical patch/with tetracaine/3-yr NC exclusivity expires 23-Jun-08

NDA# 21-717 Pliaglis topical cream/with tetracaine/3-yr NP exclusivity expires 29-Jun-09

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES * NO

*The applicant submitted a list of published studies; however, the applicant did not submit a statement that the publicly available data would not independently support approval.

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Studies 3-003-1 and 3-004-1

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 54,740

YES

!

!

! NO

! Explain:

The protocol for this study was dated 10-14-04 and conducted between 12-20-04 and 05-06-05. The clinical study report was dated 08-28-06. AlgoRx Pharma was the sponsor of IND 54,740 prior to 12-15-05, when AlgoRx merged with Corgentech. Corgentech later became Anesiva, Inc.

Investigation #2

IND # 54,740

YES

!

!

! NO

! Explain:

The protocol for this study was dated 11-18-04 and conducted between 02-03-05 and 07-14-05. The clinical study report was dated 08-28-06. AlgoRx Pharma was the sponsor of IND 54,740 prior to 12-15-05, when AlgoRx merged with Corgentech.

Corgentech later became Anesiva, Inc.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

!

!

YES

! NO

Explain:

! Explain:

See response to 4a.

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

See response to 4a.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Geri Smith

Title: Project Manager

Date: 13-Aug-07

with input from Howard Josefberg, M.D., Medical Officer

Name of Office/Division Director signing form: Sharon Hertz, M.D.

Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sharon Hertz
8/16/2007 03:02:11 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-114 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 24-Nov-06 PDUFA Goal Date: 24-Sep-07

HFD 170

Trade and generic names/dosage form: Zingo (lidocaine hydrochloride monohydrate) powder intradermal injection system

Applicant: Anesiva, Inc. Therapeutic Class: Anesthetic

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: topical local analgesia prior to venipuncture or peripheral intravenous cannulation

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 3 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: The extremities of children under 3 years of age would likely not provide adequate surface area (i.e. shape and size) to operate the Zingo device correctly, and self assessment pain measurements in pre-verbal children is difficult to achieve.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 3 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

Comments:

The sponsor enrolled three to eighteen year olds in their pivotal (and in all their pediatric) studies.

NDA 22-114

Page 3

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

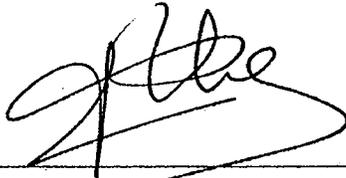
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Howard Josefberg
8/13/2007 05:14:12 PM

1.3.3 Debarment Certification

Anesiva, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



9/8/06

Daniel Gennevois, M.D.
Vice President, Medical Affairs
Anesiva, Inc.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Refer to attached list of investigators	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME John McLaughlin	TITLE Chief Executive Officer
FIRM / ORGANIZATION Anesiva, Inc.	
SIGNATURE 	DATE 9/28/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



NDA 22-114

NDA ACKNOWLEDGMENT

Anesiva, Inc.
650 Gateway Blvd.
South San Francisco, CA 94080

Attention: Christine Salido
Associate Director, Regulatory Affairs

Dear Ms. Salido:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zingo (proposed), Dermal PowderJect Lidocaine HCl Delivery System/Sterile LHM Product, topical powder, 0.5 mg

Review Priority Classification: Standard (S)

Date of Application: November 21, 2006

Date of Receipt: November 24, 2006

Our Reference Number: NDA 22-114

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 23, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 24, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

NDA 22-114

Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, contact me at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Geri Smith
Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Geraldine Smith
12/27/2006 12:15:18 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-114 Supplement # n/a Efficacy Supplement Type SE- n/a

Proprietary Name: Zingo
Established Name: lidocaine hydrochloride monohydrate powder intradermal injection system
Strengths: 0.5 mg

Applicant: Anesiva, Inc.
Agent for Applicant (if applicable): n/a

Date of Application: 11-21-06
Date of Receipt: 11-24-06
Date clock started after UN: n/a
Date of Filing Meeting: 01-10-07
Filing Date: 01-23-07
Action Goal Date (optional): 08-16-07 (Thursday) User Fee Goal Date: 09-24-07 (Monday)

Indication(s) requested: Local anesthesia prior to venipuncture or cannulation

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) n/a

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO

If yes, explain: The following lidocaine-containing drugs had unexpired exclusivity at the time of submission of this application. All contain an additional active ingredient, which is listed as well:

- NDA 21-451/Dentsply/Oraqix periodontal gel/with prilocaine/3-yr NDF exclusivity expired 19-Dec-06
- NDA 21-504/Vyteris/Lidosite topical patch/with epinephrine/3-yr NP exclusivity expired 04-May-07
- NDA 21-486/EMPI/topical solution/with epinephrine/3-yr NP exclusivity expires 26-Oct-07
- NDA 21-623/Synera/topical patch/with tetracaine/3-yr NC exclusivity expires 23-Jun-08
- NDA 21-717/ZARS/Pliglis topical cream/with tetracaine/3-yr NP exclusivity expires 29-Jun-09

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? n/a YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain: n/a

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain: (The submission contains the eCTD backbone and an HTML index.)

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic Combined paper + eNDA

This application is in: NDA format CTD format

Combined NDA and CTD formats

Does the eNDA, follow the guidance?

(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

The sponsor did not request exclusivity, but would like exclusivity if eligible.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES n/a

- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? YES NO
If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 54,740

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) November 17, 2004 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) June 19, 2006 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- invited DDMAC to labeling meetings
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? N/A YES NO

If Rx-to-OTC Switch or OTC application: n/a

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
- If no, did applicant submit a complete environmental assessment? YES NO
- If EA submitted, consulted to EA officer, OPS? (Not needed, per CMC.) YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? N/A YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 01-10-07

NDA #: 22-114

DRUG NAMES: Zingo (proposed), Dermal PowderJect Lidocaine HCl Delivery System/Sterile LHM Product, topical powder, 0.5 mg

APPLICANT: Anesiva, Inc.

BACKGROUND: Anesiva submitted this NDA under 505(b)(2) for Dermal PowderJect Lidocaine HCl Delivery System/Sterile LHM product – a device intended to deliver 0.5 mg of lidocaine HCl in powder form through the skin. The proposed indication is for local anesthesia prior to venipuncture or cannulation. This application references Synera (NDA 21-623) and Lidoderm (NDA 20-612). CDRH is also reviewing the device-related aspects of this application.

ATTENDEES: Bob Rappaport, Sharon Hertz, Howard Josefberg, Ali Al Hakim, Gary Bond, Adam Wasserman, Srikanth Nallani, Yongman Kim, Dionne Price, Pandu Soprey (CDRH), Scott A. Colburn (CDRH), Kim Compton, Geri Smith

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Howard Josefberg
Secondary Medical:	n/a
Statistical:	Yongman Kim
Pharmacology:	Gary Bond
Statistical Pharmacology:	n/a
Chemistry:	Mike Adams
Environmental Assessment (if needed):	n/a
Biopharmaceutical:	Srikanth Nallani
Microbiology, sterility:	n/a
Microbiology, clinical (for antimicrobial products only):	n/a
DSI:	
OPS:	
Regulatory Project Management:	Geri Smith
Other Consults:	CDRH, DMETS, DDMAC, SEALD, OSE, DSI

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO
No, pending receipt of remaining study reports.

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
If yes, was microbiology consulted for validation of sterilization?
(Addressed in the CDRH review.) YES NO

ELECTRONIC SUBMISSION:
Any comments: The submission is in eCTD format.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No issues have been identified.
 - Issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Geri Smith
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Lidoderm NDA 20-612 and Synera NDA 21-623

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

There are numerous pharmaceutical alternatives.

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO
(Lidoderm)

The following NDAs are some examples of pharmaceutical alternatives approved for the same indication for which the 505(b)(2) application is seeking approval:

- NDA 21-623/Endo/Synera topical patch (one of the two drugs cited as a listed drug)/indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodesiccation and shave biopsy of skin lesions
- NDA 21-504/Vyteris/Lidosite topical patch/indicated for use on normal intact skin to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions, on patients 5 years of age and older
- NDA 21-486/EMPI/topical solution/indicated for the iontophoretic production of local analgesia for superficial dermatological procedures such as venipuncture, shave removals and punch biopsies

The following NDA is an example of a pharmaceutical alternative approved for a different indication than the indication for which the 505(b)(2) application is seeking approval:

- NDA 20-612/Teikoku(Endo)/Lidoderm (one of the two drugs cited as a listed drug)/approved only for the indication of relief of pain associated with post-herpetic neuralgia

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a change in formulation from a patch to a powder.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).

YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)).

YES NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

YES NO

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.)

YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s): For Synera: 5,658,583; 5,919,479; 6,306,431; 6,465,006; 6,546,281; 6,780,426. For Lidoderm: 5,411,738; 5,589,180; 5,601,838; 5,790,869 (mis-typed in NDA -- the actual patent number is 5,709,869); 5,827,529.

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.
YES NO
If "Yes," what is the listed drug product(s)? Lidoderm and Synera
Which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug :
Module 1, section 1.12.15 and Module 2, section 2.2 (Introduction and Literature Review files under section 2.2)
Was this listed drug product(s) referenced by the applicant? (see question # 2)
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?
N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:
Version 6/14/2006

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration
21-623	001	NC	23-Jun-08

* Please note that there is no unexpired exclusivity for the other referenced drug, Lidoderm (NDA 20-612).

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Geraldine Smith
8/16/2007 02:41:32 PM
CSO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: 8/15/07

TO: Geri Smith, Regulatory Project Manager
Howard Josefberg, M.D., Clinical Reviewer
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Carolanne Currier, CSO
Good Clinical Practice Branch I

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-114

APPLICANT: Anesiva, Inc.

DRUG: Zingo (lidocaine hydrochloride monohydrate powder intradermal injection system)

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: Local anesthesia prior to venipuncture or cannulation

CONSULTATION REQUEST DATE: 3/26/07

DIVISION ACTION GOAL DATE: 8/24/07 (revised to 8/15/07)

PDUFA DATE: 9/24/07

I. BACKGROUND:

Zingo is a needle-free, single-use, disposable device/drug combination that uses pressurized helium to force Lidocaine into the skin. Zingo was submitted in NDA 22-114 by Anesiva, Inc., for use as a local anesthetic in children prior to venipuncture or cannulation. Lidocaine has been approved as an anesthetic since 1971, but the administration of Lidocaine by the pressurized delivery system has not been previously approved.

Protocols 3-003-1 and 3-004-1 were identified by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) as important studies in the NDA submission. The protocols were identical. They were multicenter, randomized, double-blind, single-dose, placebo-controlled studies, conducted in children ranging in age from 3 to 18 years. The primary efficacy variable for both studies was the child's assessment of the pain from the venipuncture or cannulation following administration of the study treatment, using the FACES pain rating scale. Safety endpoints included the occurrence of adverse events, evaluation of any skin reaction at the treatment site, and the use of concomitant medications.

Two study sites using each of the 2 protocols were selected for inspection:

Protocol 3-003-1: Drs. Jolene Bean-Lijewski, and William Zempsky.

Protocol 3-004-1: Drs. Bruce Finkel and Lawrence Sher.

These sites/investigators were selected because they enrolled large numbers of subjects, and had high rates of positive treatment response.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Jolene Bean-Lijewski, M.D.	Temple, TX	3-003-1	4/4-12/07	5/1/07	NAI
William T. Zempsky, M.D.	Hartford, CT	3-003-1	4/11-16/07	4/24/07	NAI
Lawrence Sher, M.D.	Rolling Hills Estates, CA	3-004-1	5/3-10/07	5/29/07	NAI
Bruce Finkel, M.D.	Savannah, GA	3-004-1	4/11-12/07	7/9/07	Pending (NAI*)

*Preliminary classification

Key to Classifications

NAI = No deviation from regulations.

VAI-No Response Requested= Deviations(s) from regulations.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # 3-003-1

1. Jolene Bean-Lijewski, M.D., Temple, Texas:

- a. What was inspected: At this site 98 subjects were enrolled and 93 subjects completed the study. An audit of 98 subjects' records was conducted.
- b. Limitations of inspection: None.
- c. General observations/commentary: Aside from minor record-keeping deficiencies with regard to assent forms, no problems were found with the conduct of the study or the study data. No under-reporting of adverse events was noted and efficacy data was accurately reported.
- d. Data Acceptability: The study appears to have been conducted adequately and the data generated by this site may be used in support of the respective indication.

2. William T. Zempsky, M.D., Hartford, Connecticut:

- a. What was inspected: At this site 153 subjects were screened and 152 subjects were enrolled. An audit of 51 subjects' records was conducted.
- b. Limitations of inspection: None.
- c. General observations/commentary: No problems were found with the conduct of the study or the study data. No under-reporting of adverse events was noted and efficacy data was accurately reported.
- d. Data Acceptability: The study appears to have been conducted adequately and the data generated by this site may be used in support of the respective indication.

B. Protocol # 3-004-1

1. Lawrence Sher, M.D., Rolling Hills Estates, California:

- a. What was inspected: At this site 114 subjects were screened and 111 subjects completed the study. An audit of 114 subjects' records was conducted.
- b. Limitations of inspection: None.
- c. General observations/commentary: No problems were found with the conduct of the study or the study data. No under-reporting of adverse events was noted and efficacy data was accurately reported.
- d. Data Acceptability: The study appears to have been conducted adequately and the data generated by this site may be used in support of the respective indication.

2. Bruce Finkel, M.D., Savannah, Georgia:

- a. What was inspected: At this site 55 subjects were enrolled and 53 subjects completed the study. An audit of 40 subjects' records was conducted.
- b. Limitations of inspection: None.
- c. General observations/commentary: No problems were found with the conduct of the study or the study data. No under-reporting of adverse events was noted and efficacy data was accurately reported. Observations are based on the preliminary review of the inspection report and Form FDA 483. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.
- d. Data Acceptability: The preliminary review indicates that the study appears to have been conducted adequately and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The above inspections revealed no deviations from FDA regulations and no apparent problems with data integrity. No under-reporting of adverse events was noted, and efficacy data was accurately reported. From the records reviewed, the studies appear to have been conducted adequately and may be used in support of the respective indication. An inspection summary addendum will be generated if conclusions change upon final review of the Finkel EIR.

{See appended electronic signature page}

Carolanne Currier, CSO

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Carolanne Currier
8/15/2007 01:19:57 PM
CSO

Constance Lewin
8/15/2007 01:31:03 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-114

Anesiva, Inc.
650 Gateway Blvd.
South San Francisco, CA 94080

Attention: Christine Salido
Associate Director, Regulatory Affairs

Dear Ms. Salido:

Please refer to your November 21, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zingo (proposed) Dermal PowderJect Lidocaine HCl Delivery System/Sterile LHM Product, topical powder, 0.5 mg.

We also refer to your submission dated January 4, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 23, 2007, in accordance with 21 CFR 314.101(a).

In our filing review, we identified the following potential review issue and request that you submit the following information. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

The study report for the repeated-dose study in minipigs (protocol entitled *Sterile LHM Product: A Two-Week Dermal Toxicity Study in Gottinger Minipigs[®]*) was not submitted with the NDA. As we previously agreed, you will submit the final study report to the NDA in February 2007.

In addition, we have the following comments regarding the labeling submitted in WORD format with your NDA. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider the comment as a recommendation only.

General

1. Avoid using “µg.” Instead, use “mcg.” Refer to the Institute for Safe Medication Practices web site at <http://www.ismp.org/Tools/abbreviationslist.pdf> for a list of error-prone abbreviations, symbols, and dose designations.

Highlights of Prescribing Information

2. Insert the route of administration (e.g., topical) after the drug name and dosage form. [See 21 CFR 201.57(a)(2)]
3. If a product is a member of an established pharmacologic class, the following statement must appear under INDICATIONS AND USAGE:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid and clinically meaningful to practitioners. Alternately, you may provide a rationale supporting the omission of the pharmacologic class from this section. [See 21 CFR 201.57(a)(6)]

4. The initial U.S. approval date will be the month/year that the application is approved. Replace “200X” with “mm/yy.”
5. Under CONTRAINDICATIONS, theoretical possibilities must not be listed (e.g., hypersensitivity). The description of a contraindication must explain the type and nature of the adverse reaction(s). [See 21 CFR 201.57(a)(9) and (c)(5)]
6. Under ADVERSE REACTIONS, insert Anesiva’s phone number. [See 21 CFR 201.57(a)(11)]
7. Under ADVERSE REACTIONS, remove Anesiva’s web site address (www.anesiva.com). A general customer service email address or the general company web site address cannot be used to meet the requirement of including adverse reactions reporting contact information in this section. It would not provide a structured format for reporting. [See 21 CFR 201.57(a)(11)(iv)]
8. The revision date for the first label approved under a new NDA will be the month/year that the application is approved. Replace “{Insert Month here} 200x” with “mm/yy.”

Full Prescribing Information: Contents

9. The heading for section 13 must be “NONCLINICAL TOXICOLOGY.” Please delete “(ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY)” from this heading.

Full Prescribing Information

10. Remove the bolding from the paragraph headers under the subsection headings. You may use another method for emphasis, such as italics or underlining, provided the emphasis is consistent throughout the label.
11. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The cross-reference should be in brackets. Because cross-references are embedded in the text of the FPI, we recommend the use of italics to achieve emphasis. Do not emphasize cross-references with all capital letters or bold print. [See *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products—Implementing the New Content and Format Requirements* at <http://www.fda.gov/cder/guidance/6005dft.htm>] Thus, in the DOSAGE AND ADMINISTRATION section, correct the format of the reference found at the end of the first paragraph by replacing “Refer to Instructions for Use (2.1).” with “[*see Dosage and Administration (2.1)*].”
12. In the DOSAGE AND ADMINISTRATION section, correct the reference to Figure 1. A “Figure 1” does not exist, as only Figures 1A and 1B are depicted in the labeling.
13. In the CONTRAINDICATIONS section, theoretical possibilities must not be listed (e.g., hypersensitivity). The description of a contraindication must include the type and nature of the associated adverse reaction(s). [See 21 CFR 201.57(a)(9) and (c)(5)]
14. Under CONTRAINDICATIONS, in the Device Component subsection, remove the bolding from the text.
15. Under ADVERSE REACTIONS, in the Clinical Trials Experience subsection, include the following statement preceding the presentation of adverse reactions from clinical trials. [See 21 CFR 201.57(c)(7)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
16. In the DESCRIPTION section, insert the type of dosage form and the route of administration. [See 21 CFR 201.57(c)(12)]
17. Under CLINICAL PHARMACOLOGY, under Pharmacokinetics, in the Distribution paragraph, replace “Sterile LHM Product” with Zingo, to ensure that the drug product is referred to consistently as Zingo, the proposed trade name.
18. The heading for section 13 must be “NONCLINICAL TOXICOLOGY.” Please delete “(ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY)” from this heading.

19. Delete unnecessary references. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
20. Delete "Rx Only" from the end of the labeling. This statement is not required for package insert labeling, though it is required for container and carton labeling. [See *Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*]

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, contact Geri Smith, Regulatory Project Manager, at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport

1/30/2007 06:14:19 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE
COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>ANESIVA INC Christine Salido 650 Gateway Blvd South San Francisco CA 94080 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>22114</p>
<p>2. TELEPHONE NUMBER</p> <p>650-246-6844</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>Zingo TM (Sterile LHM Product)</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006733</p>
--	---

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<p><input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)</p>	<p><input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE</p>
<p><input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act</p>	<p><input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY</p>

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

<p>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</p>	<p>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</p>	<p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</p>
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p><i>Chr Salido</i></p>	<p>TITLE</p> <p><i>Associate Director Regulatory Affairs</i></p>	<p>DATE</p> <p><i>9 October, 2006</i></p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$896,200.00



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 54, 740

Corgentech, Inc.
650 Gateway Blvd.
South San Francisco, CA 94080

Attention: Patricia Otto, R.Ph.
Vice President, Regulatory Affairs and Quality Assurance

Dear Ms. Otto:

Please refer to your Investigational New Drug Application (IND) under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Dermal PowderJect Lidocaine.

We also refer to the meeting between representatives of your firm and the FDA on June 19, 2006. The purpose of the meeting was to provide responses to your questions in your May 18, 2006, meeting package, chiefly surrounding your preparations to submit an NDA for your product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

INDUSTRY MEETING MINUTES

Meeting Date: June 19, 2006
Application Number: IND 54,740
Product: Dermal PowderJect Lidocaine
Location: White Oak Building 22, Conference Room 1311
Type of Meeting: Pre-NDA
Sponsor: Corgentech, Inc.
Proposed Indication: To provide local analgesia prior to venipuncture and intravenous cannulation
Regulatory Status: Active IND
Meeting Chair: Sharon Hertz, M. D., Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Minutes Recorder: Kim Compton, DAAARP

Industry	Title
Corgentech, Inc. Representatives	
Patricia A. Oto, R.Ph.	Vice President, Regulatory Affairs & QA
Badri Dasu	Vice President, Medical Device Engineering
Daniel Gennevois, M.D.	Vice President, Medical Affairs
Susan Kramer	Vice President, Preclinical Development
Leslie McEvoy, Ph.D.	Senior Vice President, Research
Melissa Morandi	Vice President, Quality Assurance
Jack Regan	Vice President, Manufacturing
Barbara Sheng	Director, Clinical QC
Christine Salido	Senior Manager, Regulatory Affairs
	Statistician Consultant
Michael Long, M.D.	Director of Clinical Development
FDA	Title
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Lester Schultheis, M.D., Ph.D.	Medical Officer, DAARP
Ravi Harapanhalli, Ph.D.	Chief, Branch V, Office of New Drug Quality Assurance (ONDQA)
Ali Al-Hakim, Ph.D.	Pharmaceutical Assessment Lead, Branch V, ONDQA
Gary Bond, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAARP
Srikanth Nallani, Ph.D.	Biopharmaceutical Reviewer, DAARP
Dionne Price, Ph.D.	Biostatistics Team Leader, DAARP
Yongman Kim, Ph.D.	Biostatistics Reviewer, DAARP
Jason Lipman, Ph.D.	Biomedical Engineer, CDRH
Keith Burkhart, M.D.	Medical Officer, DAARP
Janice Weiner, J.D.	Regulatory Counsel, Office of Regulatory Policy (ORP)
Kim Compton	Regulatory Project Manager
Geri Smith	Regulatory Project Manager

b(4)

Meeting Objective:

The purpose of the meeting was to provide responses to the sponsor's questions from their May 18, 2006, meeting package, chiefly surrounding their preparations to submit an NDA for their product, which has a proposed indication of providing local analgesia prior to venipuncture and intravenous cannulation.

Background:

On June 15, 2006 (prior to the June 19, 2006 meeting) the Agency forwarded to the sponsor the Agency responses to the questions. After reviewing the Agency's responses, the sponsor elected to only discuss questions 4, 5a, 20, 9a, 10a and b, 11a, 12, 14a, and b, 16, and the slide entitled "Preclinical Comments" at the meeting. The other questions and responses are included in this document following the discussions of the above listed questions for completeness but were not discussed further at the meeting on June 19, 2006.

The sponsor's questions and the FDA responses are listed in *italics*. Pertinent discussion that took place at the meeting regarding a specific question follows the question and FDA response.

Discussion of Questions:

Question 4

Scale-up operations: Corgentech Inc. proposes that the small-scale and large-scale processes at ~~---~~ and The Tech Group will be demonstrated to be equivalent by device verification and validation studies and conformance to commercial release specifications. Therefore, stability data produced from lots manufactured at the small-scale is proposed to support an identical shelf life for lots manufactured at large-scale. Corgentech Inc. will commit to submit all stability data from the large-scale process as part of the eCTD Annual Report update. Does the Agency agree that the lots manufactured at the large-scale could be granted a shelf-life which is supported by small-scale lot stability data?

b(4)

FDA Response

- *Data from the small scale process can be used to support a shelf-life for a large scale process as long as the small-scale process is deemed representative of the proposed large-scale manufacturing process with respect to the scale and process controls.*
- *However, since this is a combination product, it is expected that the batch release data from at least one large scale manufacturing process be submitted in the NDA.*
- *Stability updates may be submitted as amendments to the NDA and may continue to be submitted in the annual reports following approval of the NDA.*

Discussion of Question 4

The sponsor stated that they are working on a new facility of the same scale as their currently validated facility. They plan to move their current equipment (which is validated) in to the new facility. The ----- site will be inspection-ready at the time of NDA submission.

b(4)

The firm inquired about submitting one batch of data from the new site during the review cycle in order to have the site validated in the first quarter of 2007 (with NDA submission planned in mid to late August 2006.) Dr. Hertz stated that the Division is attempting to complete reviews earlier in the cycle in order to allow sponsors time to be able to address any questions or problems that might be uncovered once the review is complete. Therefore, having new data arrive near the end of the review cycle means there is no guarantee it will be able to be reviewed in that cycle, and it could possibly trigger an extension of the PDUFA clock.

The firm inquired about the possibility of this data being submitted as a Changes Being Effected (CBE) supplement once the NDA is approved. Dr. Al-Hakim indicated that the Division could not commit to what type of supplement is appropriate without seeing the type of information in question. Dr. Hertz stated that there is a possibility that the data could appropriately be submitted as a CBE supplement. The Division will need to see the material before being able to decide what type of supplement it would be appropriately submitted as.

Dr. Al-Hakim stated that a comparability protocol is typically submitted for review with the original NDA and can, therefore, typically avoid the need for a supplement to the NDA at a later time. He also clarified that the statements for the drug product apply to the device aspects of the product as well. Dr. Harapanhali stated that since this product is a drug-device combination, a mixture of drug and device regulations will apply. These will be determined specifically once the Agency sees the NDA.

Question 5a.

Corgentech Inc. proposes a 2-year shelf life on the Sterile LHM Product when stored at Controlled Room Temperature. Data will be submitted in the initial eCTD from a lot used in the Phase 3 clinical trials and stability data from the small-scale manufacturing processes. Corgentech Inc. will submit updated stability data approximately three months prior to the end of the initial review clock (assuming a 10 month review clock) which will include ongoing stability data from the small-scale (24 month) and commit to placing lots from the large-scale manufacturing processes on stability and report data in eCTD Annual Report update. Additionally, accelerated aging data to determine device performance and packaging integrity will be available at the time of the eCTD stability update.

b(4)

- a. *Does the Agency agree that the scope of the stability data available at the time of filing is acceptable?*

FDA Response

- *It is expected that at least three months of stability data be available for a batch manufactured at large scale either at the time of NDA submission or via a timely stability update.*
- *Since data is expected to be submitted demonstrating comparison of the two scales, it should also include stability data for the large scale batch(es).*

Discussion of Question 5

The sponsor stated that they have 24 months of real-time stability data for the combination of the drug and device, but noted that they have not validated the device facility yet. Dr. Al-Hakim stated that the NDA will need to include 3 months of device stability data. Dr. Harapanhalli stated that the sponsor will need to submit 3 months or more of accelerated data from one batch at the commercial site to bridge the data.

Question 20

Corgentech Inc. proposes to submit the device information in a PMA format in Module 3 of the eCTD in section 3.2.P. The clinical and non-clinical section of the PMA will be cross-referenced to the eCTD modules and will be in the eCTD format. The PMA section will have its own table of contents, however it will not be a stand alone document since there will be cross-references to the non-clinical and clinical modules of the eCTD. Does the Agency agree to the proposed presentation of the device information in the eCTD?

FDA Response

The proposal is acceptable as long as all the CMC information related to the device will be included in the eCTD.

Discussion of Question 20

Drs. Harapanhalli and Lipman agreed it would be acceptable for module 3 of the eCTD to be in PMA format and not integrated into the drug data.

Question 9a.

Lidocaine HCl has been widely used clinically for over 50 years and has not been determined to be carcinogenic. A minor metabolite of lidocaine, 2,6-dimethylaniline, has been found to be carcinogenic in rats; however, Corgentech Inc. proposes to reference the Agency's findings of safety for topical lidocaine use based on the LIDODERM® application based on the substantially lower dose and lack of measurable bioavailability of lidocaine HCl following use of the Sterile LHM Product compared to use of LIDODERM®, even when making adjustments for pediatric use. Literature review and nonclinical studies focused on the penetration and toxicity of non-lidocaine particulate matter show that, even under exaggerated conditions (higher pressure and loaded payloads), most emitted particles do not penetrate the skin and the

few that do are rarely seen to penetrate beyond the epidermis with few, rare particles found in the superficial dermis in human cadaver skin (not in normal pig skin) which, given the rapid turnover of the superficial dermis and epidermis, would be eliminated rapidly. Literature review and risk-analysis do not reveal any health-risk associated with dermal penetration of any of these particles.

- a. *Is the rationale and the summary information in support of not performing a carcinogenicity study acceptable to the Agency?*

FDA Response

- *Carcinogenicity studies for lidocaine are not required for this acute indication.*
- *The positive carcinogenicity data for 2,6-xylidine will not be needed for the drug product label. CDER's Executive Carcinogenicity Assessment Committee and an Anesthetic Drugs Advisory Committee both concluded that the data are not relevant for the product labeling due to different routes of administration and duration of treatment.*
- *As per previous communication, the need for carcinogenicity assessment for embedded particulates would be required only if the particulates are embedded in the skin for a long period of time. Your NDA should specifically address this issue and provide the supporting justification. Based on the information provided to date, both CDER and CDRH review teams believe that your justification for not conducting these studies based on the depth of penetration and rapid turnover of the epidermal tissues is logical.*

Discussion of Question 9a.

The sponsor stated that the particles are well below the limit specified in USP. They noted that a few of the particles were found in the epidermis when twice the planned pressure was used to deliver the product, but that there were no particles in the dermis. The sponsor indicated that they tested differing specifications for the device and used optimized particles, and even then only a few particles were observed. The sponsor stated that, because of the high rate of turnover of the skin, they feel no carcinogenicity data on the product is needed. Dr. Mellon stated that the Division and CDRH agree that if the sponsor presents the above data in their NDA submission, it will likely be acceptable to address these issues.

Preclinical Comments (Presented at the Meeting)

- *ICH Guidance for Industry, M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (July 1997) recommends that for NDA approval for human dosing of up to 2 weeks, 1 month, repeated dose studies should be conducted in 2 species (one nonrodent). For local/application site effects, the most appropriate of 2 species should be tested. This notation is consistent with meeting of October 17, 2002 in which sponsor's list of completed/planned studies included a rat intradermal study to determine fate of PC particles and to assess local reaction over a 28-day period. The Division assumes that this study will consist of daily dosing at the same site with inclusion of recovery group animals. However, in this case, the pig is the most appropriate test species. This issue should be addressed in the NDA.*

Discussion of Preclinical Comment

The sponsor stated that they have completed three multi-use studies in pigs; none with the specified paradigm though. Dr. Bond noted that none of the sponsor's studies were, by definition, true repeat-dose studies as all dosing was conducted within a short time-period during a single day, making them acute single, or multiple-dose studies. While the sponsor has a worst-case, short-term exposure scenario covered with the 12 doses being administered within 1 hour, multi-day dosing is recommended to address approval requirements for human dosing of up to 2 weeks duration. The repeat-dose testing protocol(s) can be submitted to the Division for review. The Division will respond in as timely a manner as existing workload permits. Dr. Bond noted that, while the Guidances explain what the Agency would like to see for a specific drug development plan, the sponsor is welcome to propose another plan they feel will address all the relevant issues and the Division will review it for acceptability.

Dr. Mellon stated that, if the sponsor felt that the data they had could address the issues raised in ICH M3, then the sponsor could submit their argument to that effect with the NDA. He noted that a sure way to address the issues raised in the Guidance is to do the studies as requested, but stated that the Division will review alternative proposals to address the issues.

The sponsor indicated that they planned on conducting a repeated-dose study in the pig and would submit a protocol for review.

Question 10a.

Corgentech Inc. proposes to present the two pivotal studies (3268-3-003-001 and 3268-3-004-001) as stand alone studies (data side by side) and integrated in the Summary of Efficacy. These two studies utilized a randomization process that allowed for replacement patients as defined in the protocol. The patient populations are defined as: Safety, Full Data Analysis (Intent to Treat), and Evaluable (protocol-defined).

- a. *Does the Agency agree that these two studies are pivotal and satisfy the requirement for "well-controlled" trials for the submission of an eCTD?*

FDA Response

- *These studies may be adequate and well-controlled clinical trials. It is unusual to replace subjects who drop out and it is unclear the extent to which this may impact the analysis of the ITT population.*
- *A determination of efficacy will require that the difference in pain score between the active device and the sham treatment have clinical relevance to balance any risk or discomfort from use of the product. A quantitatively small difference in the primary efficacy endpoint between treatment groups in the setting of venipuncture or intravenous catheter placement may be difficult to interpret even though it may be statistically significant.*

- *Your analysis should include an assessment of the comparability of the needle gauge between treatment arms.*

Discussion of Question 10a.

The sponsor stated that they mixed two traditional pain scales to use in their analyses because some literature reports showed that children prefer the modified faces scale for evaluation choices. Dr. Hertz stated that the sponsor will need to submit an argument that supports applying the questions from one pain scale to the pain scale presented to the patient and clarify why the combination was not validated. The sponsor will also need to explain what the differences from the two validated scales means. This will need to be addressed in the NDA submission. Dr. Rappaport stated that the Division would consult the Center's labeling and endpoint group when reviewing the sponsor's methodology.

Dr. Schultheis observed that the purpose of the analgesia of the product is to make the procedure more tolerable for the patient and improve the procedure conditions for the caregiver. If the sponsor has evidence that demonstrates this, then that would be an indicator that the product is working in some measure. The Division will need to see data that shows that there is a true clinical benefit to using the product and that the product is better than the control.

Question 10b.

Corgentech Inc. proposes to present the two pivotal studies (3268-3-003-001 and 3268-3-004-001) as stand alone studies (data side by side) and integrated in the Summary of Efficacy. These two studies utilized a randomization process that allowed for replacement patients as defined in the protocol. The patient populations are defined as: Safety, Full Data Analysis (Intent to Treat), and Evaluable (protocol-defined).

- b. *Does the Agency agree on the definitions of the patient population and presentation of these two studies?*

FDA Response

Your evaluable population includes replacement of patients who drop out before completing a venipuncture or catheter placement. If dropouts resulted from discomfort associated with administration of the Sterile LHM product or such inadequate analgesia that patients were unable to cooperate with venipuncture, then it may not be possible to establish efficacy by an analysis of a study population that allowed for replacement of patients who were discontinued. Our evaluation of efficacy will be based on the ITT population. Dropouts will then be assigned the worst possible pain rating score.

Discussion of Question 10b.

The sponsor agreed to perform the above-mentioned analysis.

Question 11a.

Corgentech Inc. proposes to define the supportive controlled studies (3268-2-002-001, 3268-4-401-001 and 3268-4-400-001) as studies that were conducted in the pediatric population utilizing a slightly different but comparable device to the device configuration for commercial supply. All other studies utilized a different device, or dose/actuation pressure than the commercial (or comparable) configuration and the data will not be integrated.

- a. *Does the Agency agree on the proposal of what studies are supportive controlled studies for the pediatric population?*

FDA Response

The evaluation of efficacy will be based on data from adequate and well-controlled trials utilizing the exact version of the device to be marketed. Studies conducted with a different version of the device or do not meet the standards described in CFR 314.126 cannot be used to support a finding of efficacy.

The review of safety will weigh the risks associated with earlier systems that are similar to the commercial device.

Discussion of Question 11a.

The sponsor believes that the two device configurations are comparable. Dr. Schultheis stated that it is unclear to the Agency that the emitted doses from both configurations were the same. The sponsor stated that they now have more data on this point and have confirmed that the emitted dose is the same. The sponsor agreed to include an outline in their submission identifying the version of the device used for each study.

Dr. Hertz stated that the Division will begin reviewing the material right away once it is submitted, and so the sponsor should submit two datasets. One dataset would consist of efficacy data pooled from adequate and well-controlled studies using versions of the device that the sponsor considers similar. The other dataset would consist of efficacy data only from studies that utilized the exact version of the device that will be marketed.

The sponsor stated that they wanted to ensure that the two phase 3 pivotal trials evaluated enough patients to stand alone if needed. Dr. Schultheis stated that the Phase 3 pivotal trials appeared to be of sufficient size.

Question 12

Data from supportive controlled trials in adults (3268-1-102-001 and 3268-1-100-001) who received the same dose with the same delivery pressure as studied in the pivotal pediatric trials (0.5 mg/20 bar) will be presented side-by-side and integrated. Both of the above adult studies used the ND5.3 device. Corgentech Inc. proposes that this data would support an indication for the adult population. Does the Agency agree on the integration

plan for the adult data, and that the data could support an indication in the adult population?

FDA Response

- *No.*
- *These studies are early exploratory evaluations of different doses. They are not adequately designed to evaluate efficacy and also do not utilize the exact version of the system that will be marketed.*

Discussion of Question 12

Dr. Schultheis stated that it was not acceptable to pool the data from different cohorts with the same doses. One of these adult studies excluded certain demographic groups while the other evaluated only a single application site and did not cover the entire age range of adults that are likely to be exposed. This suggests that these trials might not meet the criteria for adequate and well-controlled trials. The adult studies appear to have been limited in scope because they were only intended for exploratory purposes.

Dr. Schultheis stated that the Division could not agree at this point that efficacy could be extrapolated from the pediatric population to adults, but noted that it was unlikely, as there are a number of problems that would make it difficult to extrapolate and utilize the pediatric data in the adult population. The Division is looking for an efficacy study with compelling clinical evidence of a benefit to the use of the product. In addition, the studies need to address all application sites, as well as control for needle size, and cover the proposed age-range and other required demographic characteristics. The Division would consider a single trial for this purpose if it were well-designed. Dr. Hertz pointed out that such a trial would not be considered for review during the NDA review cycle unless it was received with the original submission of the application. Otherwise, it would have to be submitted as a post-approval efficacy supplement.

Question 14a.

Corgentech Inc. proposes to integrate the safety, skin tolerability, and comfort of application data for all of the studies that utilized the ND5.3 or ND5.3A device configuration (9 studies). Secondly, Corgentech Inc. proposes to present the integrated safety data from the 3 trials (3268-3-003-1, 3268-3-004-1, 3268-1-005-1) that use the ND5.3A configuration (the commercial device). Thirdly, Corgentech Inc. proposes to present the integrated safety data for the six studies (3268-2-002-001, 3268-1-100-001, 3268-1-101-001, 3268-1-102-001, 3268-4-400-001, 3268-4-401-001) that used the ND5.3 device configuration. In the Summary of Safety, the safety, skin tolerability, and comfort of application data will also be presented for the adults and the pediatric population. All other studies (14 developmental) utilized a different patient population, device or dose/pressure than the commercial configuration and safety data from these studies will be presented as stand alone and in summary tables.

- a. *Does the Agency agree with the proposal for the data to be included in the Summary of Safety?*

FDA Response

- *Your proposal to provide separate safety data tables integrated by the version(s) of device is acceptable.*
- *A comprehensive dataset from all studies conducted with similar versions of the device should be able to be electronically sorted according to the version of the device and specific characteristics that may impact safety such as the delivery pressure and the dose of lidocaine.*
- *A separate analysis of the safety data associated with the final version of the device should be provided.*

Discussion of Question 14a.

Dr. Hertz stated that the safety data should be truly integrated and include unique patient identifiers, include versions of the device used, etc. The submission should contain all of the information the Division would need to replicate the sponsor's safety conclusions and to address any new questions raised by the Agency during review of the product.

The sponsor stated that this was possible for the nine studies completed with the 5.3 and 5.3a versions of the product, but noted that earlier study data would be in summary format only and not sortable. Dr. Hertz stated that this was acceptable to the Agency.

Question 14b.

Corgentech Inc. proposes to integrate the safety, skin tolerability, and comfort of application data for all of the studies that utilized the ND5.3 or ND5.3A device configuration (9 studies). Secondly, Corgentech Inc. proposes to present the integrated safety data from the 3 trials (3268-3-003-1, 3268-3-004-1, 3268-1-005-1) that use the ND5.3A configuration (the commercial device). Thirdly, Corgentech Inc. proposes to present the integrated safety data for the six studies (3268-2-002-001, 3268-1-100-001, 3268-1-101-001, 3268-1-102-001, 3268-4-400-001, 3268-4-401-001) that used the ND5.3 device configuration. In the Summary of Safety, the safety, skin tolerability, and comfort of application data will also be presented for the adults and the pediatric population. All other studies (14 developmental) utilized a different patient population, device or dose/pressure than the commercial configuration and safety data from these studies will be presented as stand alone and in summary tables.

- b. *Are there any other analyses the Agency would require?*

FDA Response

Safety analyses should also be performed according factors that affect skin type and epidermal thickness.

Discussion of Question 14b.

Dr. Schultheis elaborated that in these analyses, the Division is looking for features that might affect mechanical resistance to ballistic penetration, noting that the outlined plan seems acceptable.

Question 16

Corgentech Inc. did not conduct clinical testing in children less than three years of age. The measures [or "variables"] used for efficacy evaluation in the pivotal trials are not validated for children less than three years of age. Additionally, the size of the footprint of the device may not be appropriate for accurate evaluation of the safety and tolerability of the Sterile LHM Product use in children younger than three. Would the Agency grant a partial pediatric waiver for the conduct of clinical studies in children less than three years of age with the Sterile LHM Product as no claim of efficacy and safety will be made in this population?

FDA Response

A rationale explaining why the device can not be scaled down for use by younger pediatric patients will be needed to consider a waiver. Deferral of studies in younger pediatric patients until after approval of the product may be considered if substantial re-engineering and testing is likely to be needed for patients younger than three years of age.

Discussion of Question 16

The sponsor stated that a study in children less than 3 years old would require a different device. Dr. Hertz stated that the sponsor could request of waiver for studies in children in that age group by submitting an argument for the Division and the Pediatric Group to review. Not having studies in this age group would not be a filing issue, as long as the full age range of the pediatric population is addressed in some way at the time of NDA filing.

Closing Discussion

Dr. Mellon stated that any study needed for review of the NDA must be submitted as complete and be the final study report version in the NDA submission.

Dr. Harapanhalli stated that the Agency is required to examine the environmental impact of the product's use as part of the NDA review, and so the sponsor should address that in their application.

The sponsor stated they were looking into the t

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The sponsor summarized their understanding of the meeting as follows (includes Action Items):

- The sponsor will have the ~~tech~~ Tech site ready for inspection at the planned time of NDA filing and will submit a comparability protocol with the NDA.
- The sponsor will include device information in Module 3, in PMA format.
- The sponsor's proposal to address imbedded particles and carcinogenicity data appears logical to the Division and the data can be updated during review.
- The sponsor will include an explanation that addresses how ICH M3 requirements were met, and if needed, submit any additional data to address ICH M3 requirements as early in the review cycle as possible.
- The sponsor will provide an efficacy analysis of the intent-to-treat population in addition to their proposed analysis of the population with replacement. The sponsor will provide detailed reasons for each patient replaced during conduct of their trials.
- The sponsor will provide their rationale for substituting questions associated with a different pain scale for the questions that have been validated for scoring on the pain scale used during their trials.
- The sponsor will include in their NDA a discussion explaining why some earlier versions of the device may be considered comparable to the final version.
- The sponsor will provide both integrated and non-integrated sets of efficacy data in the NDA submission based upon versions of the device believed to be comparable and the final version of the device, respectively.
- If earlier, but similar versions of the device are not considered comparable to the version to-be-marketed, the two pivotal Phase 3 studies conducted with the final version of the device are of sufficient size to stand alone.
- The safety data from nine studies using device versions 5.3 and 5.3a will be integrated in the application and safety information from the earliest studies will be provided in summary format only.
- Data for an adult indication should be submitted as a post-marketing efficacy supplement unless it is submitted with the original submission of the NDA.
- The sponsor's proposal to analyze their data according to skin type and epidermal thickness is appropriate.

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Large-scale processes/equipment are currently being qualified, however, this process will not be fully operational until late first quarter 2007. In order for the Agency to observe this facility/equipment in full operation and review available data, a PAI would need to be scheduled in late first quarter of 2007. Corgentech Inc. proposes to use The Tech Group for launch of the Sterile LHM Product.

- c. *Does the Agency agree that with a successful PAI, The Tech Group would be qualified to supply at initial product approval?*

FDA Response

Yes. However, for the large-scale processes to be utilized upon approval of the application to produce lots for the initial launch, the commercial site(s) should have to be inspected and should receive acceptable cGMP recommendations.

Question 5b.

Corgentech Inc. proposes a 2-year shelf life on the Sterile LHM Product when stored at Controlled Room Temperature. Data will be submitted in the initial eCTD from a lot used in the Phase 3 clinical trials and stability data from the small-scale manufacturing processes. Corgentech Inc. will submit updated stability data approximately three months prior to the end of the initial review clock (assuming a 10 month review clock) which will include ongoing stability data from the small-scale (24 month) and commit to placing lots from the large-scale manufacturing processes on stability and report data in eCTD Annual Report update. Additionally, accelerated aging data to determine device performance and packaging integrity will be available at the time of the eCTD stability update.

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- b. *Does the Agency agree on the timing of the submission of additional stability data within the review cycle?*

FDA Response

- *Stability updates should be submitted in a timely manner during the review cycle.*
- *Since, under the Good Review Management Practices (GRMPs), the reviews should be mostly completed by mid-cycle, an amendment submitted late in the cycle may or may not be reviewed depending on the volume of submission, time of submission, and available resources.*

Question 5c.

Corgentech Inc. proposes a 2-year shelf life on the Sterile LHM Product when stored at Controlled Room Temperature. Data will be submitted in the initial eCTD from a lot used in the Phase 3 clinical trials and stability data from the small-scale manufacturing processes. Corgentech Inc. will submit updated stability data approximately three months prior to the end of the initial review clock (assuming a 10 month review

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clock) which will include ongoing stability data from the small-scale (24 month) and commit to placing lots from the large-scale manufacturing processes on stability and report data in eCTD Annual Report update. Additionally, accelerated aging data to determine device performance and packaging integrity will be available at the time of the eCTD stability update.

- c. Does the Agency agree that stability data from small-scale manufacturing processes could support the proposed 2 year shelf life?

FDA Response

- The approach to computing expiration dating period appears acceptable.
- However, the review of the stability data will determine the grantable expiration dating period.
- ICH Q1E will be referenced for the extent of extrapolation beyond the real time data, if applicable.

Question 6

The film used to seal the LHM cassettes that were utilized in device lots for the Phase 3 studies and Primary Stability is no longer available from the manufacturer (~~XXXXXX~~)
There is currently an adequate supply of the film to manufacture LHM Cassettes for approximately . ——— Corgentech Inc. plans to qualify a new vendor and submit the changes in an eCTD Annual Report update. Does the Agency agree to the proposed plan to identify and qualify a new vendor and submit the change as an eCTD Annual Report update?

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FDA Response

A comparability protocol may be submitted in the NDA describing how the product made by using the film from a new vendor will be assessed to demonstrate equivalence with the product made using the approved vendor. If this protocol is assessed and deemed adequate for implementation, then the proposed change may be reported in an annual report.

Question 7

Corgentech Inc. has proposed analytical testing methods and commercial specifications for release of Drug Substance (LHM Sized Powder), Drug Product (LHM Filled Cassette), and the Final Product (Sterile LHM Product). This includes the proposal for utilizing emitted dose for a release specification instead of delivered dose. Does the Agency agree with the scope and proposed specifications for release testing for the Drug Substance, Drug Product and the Final Product?

FDA Response

- *The proposal is acceptable as you have shown that the delivered dose and emitted dose are not significantly different.*
- *However, it is recommended that delivered and emitted dose test be performed on final product (Sterile LHM) in the initial NDA validation batches.*

Question 19

Corgentech Inc. proposes to describe the Drug Substance (LHM Sized Powder) and Drug Product (LHM filled cassette) in the CMC section (Module 3) of the eCTD. Additionally, the detailed information of the lidocaine, USP manufacturing process (section 3.2.S) performed by [redacted] will be cross-referenced to the closed-section of the DMF that is not on file with Corgentech Inc. However, the details of the sizing process performed by [redacted] on the bulk lidocaine will be included in the eCTD. Does the Agency agree with the proposed presentation and the cross-referencing to the DMF of the CMC information in the eCTD?

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FDA Response

Yes

Chemistry and Device Comments (Presented as part of the Agency Response)

- *A well documented pharmaceutical development report, as per ICH-Q8, should be included in the NDA submission.*
- *The names and addresses of manufacturing sites involved in the manufacturing, release, and stability testing should be provided in the NDA, including their registration numbers.*

Question 8a.

Corgentech Inc. proposes to submit an eCTD as a 505(B)(2) application covered under the Food, Drug, and Cosmetic Act. The eCTD will include safety and efficacy studies that have utilized the device and will also reference information that that will come from studies not conducted by or for Corgentech Inc. and for which Corgentech Inc. has not obtained a right of reference to the raw data. The choice of the reference product is LIDODERM®. Corgentech Inc. proposes to reference the Agency's findings of safety only (not efficacy) of LIDODERM® based on the substantially lower dose and lack of measurable bioavailability of lidocaine HCl following use of the Sterile LHM Product compared to use of LIDODERM®, even when making adjustments for pediatric use. A comprehensive literature search of topical dermal lidocaine use, a brief summary of the known toxicology associated with systemic exposure of lidocaine, and a literature review of the safety and toxicity of non-lidocaine particulate matter which may be inadvertently introduced into the surface layers of the skin during normal use and abuse conditions will also be included in the eCTD. All other safety data will be referenced to the Agency's review on LIDODERM®.

a. *Does the Agency agree that LIDODERM® is an acceptable product to reference?*

FDA Response

- *Your selection of Lidoderm (NDA 20-612) as a reference drug product is acceptable provided you include adequate patent certification at the time of NDA submission.*
- *The nonclinical information in the Lidoderm labeling pertaining to impairment of fertility and reproduction and developmental toxicity is not as complete as other lidocaine topical products. Additional data may be available to provide a more complete drug label for your product. Based upon your review of the literature and other products, you are encouraged to submit a update the labeling.*
- *The Agency noted that your summary table on page 88 of the preNDA meeting package references both the Lidoderm and EMLA package insert. You may reference data from more than one NDA; however, you must provide adequate patent certification for each referenced product at the time of NDA submission.*

Question 8b.

Corgentech Inc. proposes to submit an eCTD as a 505(B)(2) application covered under the Food, Drug, and Cosmetic Act. The eCTD will include safety and efficacy studies that have utilized the device and will also reference information that that will come from studies not conducted by or for Corgentech Inc. and for which Corgentech Inc. has not obtained a right of reference to the raw data. The choice of the reference product is LIDODERM®. Corgentech Inc. proposes to reference the Agency's findings of safety only (not efficacy) of LIDODERM® based on the substantially lower dose and lack of measurable bioavailability of lidocaine HCl following use of the Sterile LHM Product compared to use of LIDODERM®, even when making adjustments for pediatric use. A comprehensive literature search of topical dermal lidocaine use, a brief summary of the known toxicology associated with systemic exposure of lidocaine, and a literature review of the safety and toxicity of non-lidocaine particulate matter which may be inadvertently introduced into the surface layers of the skin during normal use and abuse conditions will also be included in the eCTD. All other safety data will be referenced to the Agency's review on LIDODERM®.

b. *Is the scope of the proposed non-clinical literature search on lidocaine acceptable to the Agency?*

FDA Response

- *We recommend that you conduct a comprehensive literature search to identify any safety concerns with respect to all components of your drug product (e.g., active ingredient, particulates, impurities, etc.).*

- *For lidocaine, the Division specifically notes that information pertaining to reproduction and developmental toxicity be included. Please submit copies of all referenced literature with the NDA submission.*

Question 8c.

Corgentech Inc. proposes to submit an eCTD as a 505(B)(2) application covered under the Food, Drug, and Cosmetic Act. The eCTD will include safety and efficacy studies that have utilized the device and will also reference information that that will come from studies not conducted by or for Corgentech Inc. and for which Corgentech Inc. has not obtained a right of reference to the raw data. The choice of the reference product is LIDODERM®. Corgentech Inc. proposes to reference the Agency's findings of safety only (not efficacy) of LIDODERM® based on the substantially lower dose and lack of measurable bioavailability of lidocaine HCl following use of the Sterile LHM Product compared to use of LIDODERM®, even when making adjustments for pediatric use. A comprehensive literature search of topical dermal lidocaine use, a brief summary of the known toxicology associated with systemic exposure of lidocaine, and a literature review of the safety and toxicity of non-lidocaine particulate matter which may be inadvertently introduced into the surface layers of the skin during normal use and abuse conditions will also be included in the eCTD. All other safety data will be referenced to the Agency's review on LIDODERM®.

- c. *Does the Agency agree that the LHM Sterile Device can be filed as a 505(B)(2) application using LIDODERM® as the Reference Product?*

FDA Response

See response to question 8a.

Question 9b.

Lidocaine HCl has been widely used clinically for over 50 years and has not been determined to be carcinogenic. A minor metabolite of lidocaine, 2,6-dimethylaniline, has been found to be carcinogenic in rats; however, Corgentech Inc. proposes to reference the Agency's findings of safety for topical lidocaine use based on the LIDODERM® application based on the substantially lower dose and lack of measurable bioavailability of lidocaine HCl following use of the Sterile LHM Product compared to use of LIDODERM®, even when making adjustments for pediatric use.

Literature review and nonclinical studies focused on the penetration and toxicity of non-lidocaine particulate matter show that, even under exaggerated conditions (higher pressure and loaded payloads), most emitted particles do not penetrate the skin and the few that do are rarely seen to penetrate beyond the epidermis with few, rare particles found in the superficial dermis in human cadaver skin (not in normal pig skin) which, given the rapid turnover of the superficial dermis and epidermis, would be eliminated rapidly. Literature review and risk-analysis do not reveal any health-risk associated with dermal penetration of any of these particles.

- b. *Does the Agency agree that a chronic carcinogenicity study is not required for registration of the Sterile LHM Product?*

FDA Response

See response to 9a.

Preclinical Comments (Presented as part of the Agency Response)

- *For the NDA submission, any impurity or degradation product that exceed ICH thresholds should be adequately qualified for the NDA submission (ICHQ3A, ICHQ3B(R)).*
- *Adequate qualification should include:*
 - *Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay*
 - *Repeat dose toxicology of appropriate duration to support the proposed indication.*
- *The NDA submission should contain information on potential leachables and extractable from the drug delivery system. Provide your justification for the safety of potential exposure to the study participants, including supporting data/literature references. Complete characterization of leachables and extractables should be submitted with the NDA.*

General Comments: 505(b)(2) Applications (Presented as part of the Agency Response)

- *505(b)(2) applications must clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference.*
- *A 505(b)(2) application that relies upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.*
- *A 505(b)(2) application relying upon literature must clearly identify the listed drug(s) on which the studies were conducted (if any).*
- *For a 505(b)(2) application you must provide a patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). -- (Listed in the Orange Book)*

- *Patent certification should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.*
- *Note the following key issue regarding the requirement for appropriate patent certification: Due to legislation contained in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), if during the review of an NDA filed under 505(b)(2), either the applicant decides to refer to a different product than that/those identified in the original application, or the Agency discovers that the applicant did not appropriately certify to the patent(s) of the products referenced in the original application, then the applicant would be required to withdraw and resubmit the application as a new original NDA, with the appropriate Patent Certifications included, potentially requiring a new User Fee.*
- *Before submitting your NDA, the guidance recommends that you submit a plan to the reviewing Division that specifically identifies the types of bridging studies that will be conducted. You should also identify those components of its application for which you expect to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The Division will critique the plan and provide guidance.*
- *The review of this plan will be completed around Division deadlines that may take higher priority; therefore, the Division encourages that you submit such a plan well in advance of the NDA submission, to provide adequate time for the reviewer to evaluate the proposal and resolve any potential concerns that may result in a filing issue or delay in the review process.*
- *You must also submit a relative bioavailability study comparing the proposed product to the listed drug(s) (if any) if there are measurable systemic levels.*
- *If the only literature that you submit is within the public domain and/or you have right of reference to the studies and the data required to support them, you may be able to submit a 505(b)(1) application.*
- *If portions of your application rely upon studies that you do not have right of reference to or are not within the public domain, you must submit a 505(b)(2) application. Please note that not all studies reported in the literature are supported by data that exists within the public domain. Many studies in the literature are supported by proprietary data.*

Question 17

Pharmacokinetic data were obtained utilizing the ND5.3 device in 38 healthy adults (Study 3268-1-101-001). Data demonstrated no detectable levels above the limit of quantitation (5.0 ng/mL) of lidocaine in blood after 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180 and 240 minutes of dose administration. Based on the low dose, prediction that plasma levels will be undetectable, and ethical considerations of subjecting pediatric patients to unnecessary venipuncture, no further pediatric PK studies are planned. Corgentech Inc. proposes to reference the Agency's finding of safety only (not efficacy) of LIDODERM® based on the substantially lower dose and substantially lower

bioavailability of lidocaine HCl following use of the Sterile LHM Product compared to use of LIDODERM®, even when making adjustments for pediatric use. Based on the lack of measured systemic lidocaine exposure following use of the Sterile LHM Product, Corgentech Inc. is proposing that a head-to-head bioavailability study to support the 505 (B)(2) application is not warranted. Does the Agency agree that pharmacokinetic data in a pediatric population and a bioavailability study are not required for registration of the LHM Device under a 505 (B)(2) application?

FDA Response

Yes.

Question 18

Corgentech Inc. proposes to include SAS XPORT transport format datasets for clinical studies that are pivotal studies or are controlled supportive studies using the most recent device/dose/pressure configurations (ND5.3 and ND5.3A). This includes all nine studies presented in the Summary of Efficacy/Summary of Safety. All other developmental studies (14 studies) are considered supportive as they utilized very different devices/doses/pressures. Most of these early studies do not have available electronic datasets in the formats required for an eCTD and will not be submitted. These development reports are proposed to be submitted as stand alone reports with all of the data listing/tables in Word or pdf format. Does the Agency agree on the proposal for the submission of the datasets and the 14 development reports?

FDA Response

Yes, we agree with the proposal. In addition, all derived and raw data should be included in the SAS transport datasets for the pivotal and controlled supportive studies. You should also include detailed descriptions of variables and variable values used in the SAS datasets.

Question 11b.

In the Summary of Efficacy, it is proposed to integrate and analyze data from the two pivotal studies with the three supportive studies where the same dose (0.5 mg), pressure (20 or 21 bar) and pain scale (Wong-Baker and VAS) were used.

b. Does the Agency agree to this integration plan for the data from pediatric studies?

FDA Response

- No.*
- Only data from your adequate and well-controlled trials conducted with the commercial version of the device should be integrated in your efficacy analysis.*

Question 13

Does the Agency agree with the proposal for the data presentation for the Summary of Efficacy? Are there any other analyses the Agency would require?

FDA Response

- *You propose to summarize the results of the individual studies and to integrate the results from pediatric and adult studies, separately. As stated in previous responses, you should only include studies that are useful in the evaluation of efficacy.*
- *The purpose of the (integrated) summary of efficacy is to explain how the results of the individual studies support the claims being made. In the case of conflicting study results, additional analyses may be necessary.*

Question 15

Corgentech Inc. proposes to include the CRFs for deaths and drop-outs for the nine studies included in the integrated Summary of Safety. All other CRFs would be available upon request. Corgentech Inc. proposes to include the CRFs for deaths and drop-outs for the nine studies included in the integrated Summary of Safety. All other CRFs would be available upon request. Is this proposal for the submission of the CRFs for deaths and drop-outs acceptable to the Agency?

FDA Response

Case report forms should also be provided for serious adverse events. Case reports for severe reactions, especially descriptions of local tissue injury are likely to be requested. A brief text summary of each submitted case report can be helpful during the review.

Question 21

Does the Agency agree with the proposed Overall Table of Contents for the eCTD?

FDA Response

In regard to nonclinical sections, an eCTD submission requires Module 2 sections 2.4 (nonclinical overview) and 2.6 (nonclinical written and tabulated summaries), and Module 4 (study reports – original data and/or literature publications).

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/s/

Kimberly Compton
7/17/2006 08:14:17 PM



IND 54, 740

AlgoRx Pharmaceuticals, Inc.
500 Plaza Drive
Secaucus, NJ 07094

Attention: Jeffrey D. Lazar, M.D., Ph.D.
Senior Vice President, Clinical Research and Regulatory Affairs

Dear Dr. Lazar:

Please refer to the End-of-Phase 2 meeting between representatives of your firm and FDA on November 17, 2004. The purpose of the meeting was to provide you with responses to your questions concerning the your Phase 3 development plans for Dermal PowderJect Lidocaine product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7432.

Sincerely,

{See appended electronic signature page}

Kimberly Compton
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: November 17, 2004

Location: Parklawn Building, Chesapeake Conference Room

Sponsor: AlgoRx Pharmaceuticals, Inc.

IND: 54, 740

Drug Name: Dermal PowderJect Lidocaine

Type of Meeting: Type B, End-of-Phase 2

Meeting Chair: Rigoberto Roca, M.D.
Division of Anesthetic, Critical Care and Addiction Drug Products

Minutes Recorder: Kimberly Compton, Regulatory Project Manager

Industry	Title
AlgoRx Representatives	
Ronald Burch, M.D., Ph.D.	President and CEO
Jeffrey Lazar, M.D., Ph.D.	Senior Vice President
Anil Dasu, M.S.	Vice President
Patricia Richards, M.D., Ph.D.	Medical Director
Elizabeth Vause, B.S.	Senior Director
	Consulting Statistician
	Consulting Toxicologist
Paula Buckley, B.S.	Director, QA/QC
Dianne Sykes	Project Manager, Clinical
FDA	Title
Bob Rappaport, M.D.	Division Director
Rigoberto Roca, M.D.	Deputy Division Director
Lex Schultheis, M.D., Ph.D.	Medical Officer
Ravi Harapanhalli, Ph.D.	Chemistry Team Leader
Eric Duffy, Ph.D.	DNDC II, Director
Suzanne Thornton-Jones, Ph.D.	Pharmacology/Toxicology Reviewer
Dan Mellon, Ph.D.	Supervisory Pharmacologist
David Lee, Ph.D.	Biopharmaceutical Reviewer
Jason Lipman, Ph.D.	Biomedical Engineer, CDRH
Pandu Soprey, Ph.D.	Microbiologist, CDRH
Kim Compton	Regulatory Project Manager
Robert Shibuya, M.D.	Medical Officer
Teisha Taylor	Pharm.D. Candidate

b(4)

Meeting Objective: To provide the sponsor with responses to their questions concerning the Phase 3 development of their Dermal PowderJect Lidocaine product.

Procedural Note

A copy of the Agency's preliminary responses to the sponsor's questions was forwarded to the sponsor prior to the meeting.

The sponsor's questions are listed in *Italics* with the FDA responses presented at the meeting following. Pertinent discussion that took place at the meeting regarding a specific question will follow the question and FDA response.

General Discussion:

Dr. Rappaport stated that a future Chemistry/Device meeting would be acceptable.

Question 2.1

AlgoRx would like to use emitted dose as the sole measure of lidocaine delivery for finished product release purposes. An analysis of the emitted dose and delivered dose may be found under tab 5. Does the Agency concur?

FDA Response

- Emitted and delivered dose should be determined. Note that for labeling, the dose expressed will be the emitted dose.
- Provide a target (% label claim) for the emitted dose.
- The ALGRX 3268 ND5.3A device is planned for the proposed Phase 3 studies and the data indicates that the mean emitted dose was 76.3 % of the nominal 0.5 mg/dose with a standard deviation of 5.8 %. As indicated in the meeting minutes of the meeting dated February 13, 2003, the acceptance criteria for the emitted dose uniformity would be based on clinical batch performance using this device at specified pressure.
- The total percent recovery of lidocaine HCl was typically less than 100% and the balance of the drug dose is presumed to be lost within the device components other than the drug cassette (such as nozzle and silencer cut, etc). Provide data accounting for 100% mass balance.
- All outstanding CMC issues listed in the meeting minutes of the above dated meeting should be addressed during Phase 3 studies.

Discussion of Question 2.1

The sponsor stated that the device is a single-use, pre-filled, disposable product, with no intent on the part of the sponsor to adapt or market the product for multiple use.

Question 2.2

AlgoRx has collected a significant amount of stability data on ALGRX 3268 drug product at 25°C/60% RH, 40°C/75% RH and 30°C/60% RH. AlgoRx plans on placing the pivotal batches on a long-term stability program at the above storage conditions with one change; the intermediate storage condition of 30°C/60% RH will be changed to reflect the ICH change to 30°C/65% RH. Based on the data obtained, AlgoRx would like to submit 6 month data at the 30°C/65% RH storage condition at the time of submission of the NDA package to satisfy an expiration dating of 24 months. AlgoRx agrees to furnish updated reports as the data are obtained through 24 months. Does the Agency agree?

FDA Response

- The Agency expects to see 12 months of long-term stability data at the time of NDA submission or during the review cycle. Stability updates are encouraged not beyond the last three months of the review clock.
- The Agency will consider ICH Q1E guidelines for the extrapolation of the shelf life beyond the available real-time data.
- The data for all stability-indicating attributes should be amenable for statistical analysis and should support the proposed shelf-life.
- Supporting stability data and data on the degradation pathways for the drug product should be submitted to support shelf-life extrapolation.
- It is recommended that you determine whether the device performance is changed if it is kept at elevated temperature prior to use (e.g. at body temperature.)

Discussion of Question 2.2

The sponsor agreed to submit another six months of stability data before the three-month mark of the review cycle. The data should be submitted in SAS transport file format. The sponsor also stated that they would address what effects, if any, carrying the product in one's pockets would have on the device's characteristics by accessing the performance within body temperature ranges.

Dr. Harapanhalli stated that the stability data from device version 5.3 could be supportive for version 5.3A.

Question 2.3

As indicated in IND Amendment on April 26, 2003, serial # 33, the phase III program will utilize the ND 5.3A system. Design changes were identified in that amendment. Does the Agency agree that these design changes can be utilized in Phase III?

FDA Response

The descriptions of the five modifications between devices ND5.3 and ND 5.3A are too general (i.e., improve reliability, improve consistency).

- Provide additional information as to how the changes affect the device.

- Be sure to address which specific device functions have "improved reliability" and "improved consistency".
- This information is needed before a full response to this Question can be provided.

Discussion of Question 2.3

It was agreed that much of the CMC/device related issues would be discussed in greater detail at a follow-up CMC/device meeting. The sponsor noted that the language regarding improved reliability and consistency was from the investigator's brochure and was not intended to ever appear in any technical amendment for the product.

Question 2.4

As the data from the key "device characterization" studies become available, we would like FDA agreement that a separate device and CMC meeting will be held in the future. Does the Agency agree?

FDA Response

- An additional meeting should be justified.
- As indicated earlier, all outstanding CMC issues raised during earlier meetings should be addressed.
- Specifically, data on particle size distribution and other characterization studies should be provided linking design changes. See Device-Related Comments.

Discussion of Question 2.4

Dr. Harpanhalli stated that the sponsor should include data bridging the two devices (5.3 and 5.3A).

Device-Related Comments (Slide presented at the meeting)

- On page 20 and 21, Questions 3 and 4, the risks associated with permanent implantation of materials that are ejected from the device are addressed. Several reports that address this issue were referenced. However, CDRH has not yet reviewed these reports. Therefore, if it has not already been addressed, discuss how the biocompatibility testing that was performed compares with the test methods described in ISO 10993.
- Provide further explanation of the helium microcylinder addressing the following:
 - the pathway that the helium travels when the microcylinder tip is broken until it reaches the drug cassette (i.e. does helium escape from the broken tip, how does the helium fill the expansion chamber, does helium leak past the button);
 - the reliability of the microcylinder to both initiate the release of helium and release helium at the desired pressure range;
 - the injection pressure range associated with the nominal helium pressure of 20 bar;

- the range of force required to break the microcylinder tip;
- the method for retaining the microcylinder in the device;
- the shelflife of the microcylinder (i.e. is there a reduction in pressure over time)
- Indicate how loud, in decibels, the injection from the ND5.3A device is.
- Confirm that the Phase 3 clinical studies will use the ND5.3A device at a pressure of — a payload of 0.5mg, and a particle size of —
- On page 164, it states that studies have been conducted with both human and pig cadaver skin which characterized and quantified the type of particle and its depth of penetration. Clarify whether this testing was done at the pressure, payload, and particle size intended for Phase 3 study. In addition, provide the results from this testing, including range of both depth of penetration and injected particle size.
- On page 2, Question 4, it is indicated that future meetings to discuss data from “device characterization” studies would be desired. Clarify what types of data are being referred to.

b(4)

Discussion of Device-Related Comments

Dr. Lipman stated that the ISO 10993 was the standard used by the device review team when addressing bioavailability issues for devices. The sponsor agreed to review ISO 10993 and provide additional information on how their biocompatibility testing compares with the testing described in ISO 10993.

The sponsor indicated that some of the requested information may have been submitted in Serial 033 and will provide the references.

The Agency will retrieve archival copies of the submission for internal dissemination; however the sponsor may choose to resubmit a copy of the submission to expedite access. Dr. Lipman outlined the following points from the presented slide comments where additional information or clarification is still needed:

- the pathway that the helium travels when the microcylinder tip is broken until it reaches the drug cassette (i.e. does helium escape from the broken tip, how does the helium fill the expansion chamber, does helium leak past the button); (*Serial # 033 contains some of this information, but additional information would be helpful.*)
- the reliability of the microcylinder to both initiate the release of helium and release helium at the desired pressure range; (*The Agency noted that additional information on this issue would be helpful.*)
- the injection pressure range associated with the nominal helium pressure of 20 bar; (*The Agency noted that additional information on this issue would be helpful.*)

- the range of force required to break the microcylinder tip; (*The Sponsor agreed to provide additional information on this issue.*)
- the method for retaining the microcylinder in the device; (*The sponsor believes Serial 033 should contain this information.*)
- the shelflife of the microcylinder (i.e. is there a reduction in pressure over time). (*The Agency noted that additional information on this issue would be helpful.*)

The sponsor agreed to provide additional failure rate information about nozzle retention features to supplement the information contained in serial # 033 regarding device modifications.

The sponsor stated that the noise level of the product is between 115-130dB and is within the acceptable range according to relevant standards. Submission of information to confirm these comments would be helpful to the Agency.

The sponsor confirmed that the Phase 3 clinical studies will use the ND5.3A device at a pressure of — , a payload of 0.5mg, and a particle size of —

b(4)

The device review team will await the request for a follow-up CMC/device meeting. The sponsor agreed to bring a sample of the device to the next meeting.

Question 1.1

We believe that there are no outstanding pharmacology and toxicology issues. An overview of the status of the program will be provided in the briefing package. Does the Agency agree that no additional pharmacology/ toxicology studies are needed to support an eventual NDA filing?

FDA Response

- No.
- Provide information regarding duration of particle deposition in the skin for lidocaine, as previous requested. The information can be provided from a review of the literature or from a non-clinical study.

b(4)

Discussion of Question 1.1

The sponsor confirmed for Dr. Mellon that the final device will function as a single-pressure/single-payload device. The Sponsor also indicated that they would submit a table summarizing all non-clinical studies, payload, pressure, and other pertinent information for ease of review.

Dr. Thornton-Jones stated that since the sponsor is still conducting stability testing, if they discover any impurities or degradants at the 12-month mark that are outside the ICH limits of acceptability, the sponsor will either need to qualify the impurities/degradants according the ICH-Q3A and/or ICH-Q3B guidances, or lower their amount below the acceptable limit. Dr.

Mellon noted that, depending on when the stability data is submitted in the review cycle, the initial expiration dating of the product might be limited.

Question 3.1 (a)

Our Phase 2 results indicate that a single configuration (0.5 mg/20 bar) is both safe and effective at both the back of the hand and the antecubital fossa. The studies also indicate that there is minimal skin reaction post-administration of the 0.5 mg/20 bar configuration in children ages 3-18 and adults, and skin reaction are in general mild and the majority resolve within the first 30 minutes after administration. Based on these results (see tab 6 for a review of the integrated safety and efficacy data), we intend to conduct two identical 500 subject studies in Phase 3. These protocols will include children aged 3 to 18, just as in our Phase 2 trials. This will give total numbers of exposure as shown in the table, below. The protocol for the Phase III program is provided under Tab 7.

Subject to review of the data submitted, does FDA agree with our choice of 0.5 mg/20 bar as the single configuration to be carried forward?

FDA Response

This configuration may be appropriate for use in the age group and the anatomic locations previously tested in the sponsor's completed studies. Alternate anatomic locations or use in ages groups not studied may require changes to the configuration of the delivery system.

Question 3.1 (b)

Does FDA agree, subject to review of and agreement upon the protocol, that this will be sufficient for the previously agreed upon 505(b)(2) NDA submission?

FDA Response

- It may be appropriate to reference preclinical or clinical information about the safety of systemic exposure to lidocaine.
- The pivotal clinical trials are expected to be similar regardless of whether a 505(b)(2) is used or not. You may need to extend the data in certain populations where little data is available, such as in patients less than 3 years old.

Question 3.1 (c)

Does FDA agree that subjects can be discharged after observation of the skin site 30 minutes post-administration of ALGRX 3268, provided there is no erythema or edema greater than grade 2 or hemorrhage or petechiae greater than grade 3? Further, does FDA agree that telephone contact within 2-4 days is adequate follow-up?

FDA Response

This proposal may be acceptable provided that the patient's guardian is provided with clear guidance enabling them to detect evidence of an emergent or worsening adverse event and there is provision for professional examination and treatment if needed.

Question 3.2

We wish to discuss the impact of "The Pediatric Rule" on our Phase 3 program and on the eventual NDA. The Phase 2 studies conducted in adults with ALGRX 3268 (model ND 5.3) were adequately powered and definitively indicated the time of onset and duration of effect. Thus, we believe that additional studies in adults are not needed. Thus, key Phase 3 studies will be conducted in children from age 3 to 18 years. As previously discussed with FDA, we have chosen 3 years as the lower limit to be fully consistent with the Xylocaine® label, which does not mention children below this age. We also recognize that the Agency has the prerogative to waive all or some portions of the requirements of The Pediatric Rule. Does FDA agree that our program meets the spirit of The Pediatric Rule and that a partial waiver can be granted to waive the need to study the drug in younger children, infants, and neonates?

FDA Response

- The "Pediatric Rule" was supplanted by the Best Pharmaceuticals for Children Act. (<http://www.fda.gov/opacom/laws/prea.html>)
- A request for waiver should be based upon a scientific rationale that makes study in pediatric patients unnecessary. The agency has reason to expect that this product may be used in patients less than 3 years of age. Although the lidocaine label does not reference information about patients younger than 3 years old, we will require clinical trials with this product unless you can provide a compelling rationale why they are unnecessary.

Discussion of Question 3.2

Dr. Schultheis stated that no written explanation of the rationale precluding the use of the product in children less than three year old has been submitted. He stated that, unless the sponsor could provide compelling support (i.e., safety, anatomical impossibility, etc.) for an argument why it should not be used, the Agency believes it should be studied over the full age range of the pediatric population.

Question 4.0

We anticipate an NDA filing in late 2005. We currently plan on filing in traditional NDA format. We are not planning on an electronic filing. Is this approach acceptable to FDA?

FDA Response

- It is acceptable, however, electronic submission, especially one in eCTD format is highly recommended.
- Stability data within the CMC section, and data tables and datasets should be provided in SAS transportable format.
- Labeling is required to be submitted electronically.

Discussion of Clinical Comments

The sponsor stated that they would address the issue of phototoxicity in a written response to the Agency.

Dr. Thornton-Jones stated the Agency needs to know how to address the issues of particle deposition into the stratum corneum in the product labeling, as the labeling will need to tell patients what to expect after using the product. The Agency is not concerned about lidocaine as it does not absorb within the UV light spectrum and rapidly disperses within the skin. The concern for phototoxicity is for the other particles, such as [redacted] that are deposited into the skin. It would be acceptable to expose cadaver skin following delivery of these products with the device and check for absorption within the [redacted] range of the light spectrum. If there is no absorption in this range of the spectrum then the Sponsor should include the results and a rationale for not conducting phototoxicity studies in the NDA. The sponsor agreed to address this issue.

b(4)

Closing Discussion

Dr. Mellon encouraged the sponsor to examine their submission plan of a 505(b)(2) application, and encouraged them to submit their plan for what items will be referenced as early as possible so it can be reviewed by the Agency.

The sponsor clarified that they were currently only targeting a pediatric indication and Dr. Rappaport stated that, if that were the case, data on use of the product in the geriatric population would not be needed. However the sponsor's package will need to include a sound justification for why the product should only be indicated for the pediatric population. The sponsor's justification should also include a component supporting the contention that, if the product were approved only for a pediatric population, it would not be used in a broader population, eventually.

Dr. Rappaport stated that even if the sponsor were only targeting an indication in the pediatric population, they would still be required to submit data on the use of the product in different skin types. The sponsor stated that they would ensure all demographics were well represented in the studies.

Dr. Lee pointed out that all of the PK data collected thus far is from adults and that, if the sponsor were going to target a pediatric population, the Agency would require PK data in pediatric subjects. Dr. Lee agreed that the sponsor could submit literature information on the PK of lidocaine in pediatric patients as a background, but noted that the sponsor will need to demonstrate that the device does not deliver systemic levels of the drug. Dr. Rappaport added that, alternatively, the sponsor could provide a rationale that it would be impossible to obtain systemic levels of the drug. He suggested the sponsor begin examining this issue now and submit a package to the Agency for review of its acceptability.

The sponsor summarized their understanding of the meeting and action items as follows:

- The sponsor will need to clearly outline the body temperature ranges the product might be temporarily stored at while in clothing pockets and provide data on the product performance in that range.
- The sponsor will need to submit information on the amount of force required to depress the actuation button.
- The sponsor will provide the requested additional information not included in serial # 033, as outlined in the discussion of Device-Related comments.
- The sponsor will provide data on the noise factors associated with the product.
- The Agency will provide information to the sponsor on where to obtain additional information on human factors.

*****Post- Meeting Note-** Dr. Lipman refers the sponsor to the following website to obtain human factors information, including design requirements stated in the Code of Federal Regulations (*Quality System Regulation*), relevant *Human Factors Guidance* documents, and recognized *Human Factors Standards*: <http://www.fda.gov/cdrh/humanfactors/index.html>. Links to this information will be found under the subheading *Information for Manufacturers and Distributors*.

- The sponsor will provide a plan on how the issue of particles will be addressed for the DMF/NDA, which will be discussed at the CMC/device meeting.
- The discussion of the details of version 5.3 *versus* 5.3A will be deferred until the CMC/device meeting.
- The sponsor will review ISO 10993 and the CDRH review team will review the relevant information already submitted to the Agency.
- The sponsor will provide a summary table of completed and planned studies.
- The sponsor will provide information garnered from collected data and from the literature on particle duration in the skin.
- The sponsor will study the Agency guidance on 505(b)(2) applications and submit a plan for what materials they plan to reference in their NDA.
- The sponsor's plan for the traditional format of their NDA (with the specific items discussed being submitted electronically) is acceptable.
- The sponsor will provide an argument for their product not being utilized (and therefore not studied) in patients less than 3 years old.
- The sponsor agrees to study phototoxicity issues in cadaver skin.

Minutes prepared by: Kim Compton

Minutes concurred by Chair: Rigoberto Roca, M.D.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Compton
12/14/04 04:18:17 PM

ACTION PACKAGE CHECKLIST

BLA # NDA # 22-114	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Zingo Established Name: lidocaine hydrochloride monohydrate Dosage Form: powder intradermal injection system		Applicant: Anesiva, Inc.
		Division: 170 Phone # 301-796-2204
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NDA 20-612, Lidoderm NDA 21-623, Synera</p> <p>Provide a brief explanation of how this product is different from the listed drug. The dosage form (topical patch) of the referenced drugs differs from that of Zingo, as Zingo is a powder intradermal injection system. Also, Synera contains two active ingredients (tetracaine and lidocaine), whereas Zingo contains only lidocaine. Further, the amount of lidocaine delivered by Zingo is less than that available from Lidoderm or Synera.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 13-Aug-07</p>
❖ User Fee Goal Date		24-Sep-07
❖ Action Goal Date (if different)		16-Aug-07
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3 NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> • Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) • OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	<p>The answers provided in this section apply to each of the paragraph IV certifications.</p>
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	<p>Deputy Director: 16-Aug-07</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>✓</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	<p>✓</p>
<p>❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> DMETS 03-Aug-07 <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 23-Mar-07 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	16-Aug-07
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	✓
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	<input type="checkbox"/> No mtg 19-Jun-06 <input type="checkbox"/> No mtg 17-Nov-04
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	<input checked="" type="checkbox"/> No AC meeting
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	14-Aug-07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>) CDRH	<input type="checkbox"/> None 03-Aug-07
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	14-Aug-07 (part of CMC review)
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 12-Jun-07 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	30-Jul-07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
❖ Clinical review(s) (<i>indicate date for each review</i>)	06-Aug-07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	06-Aug-07 (in clinical review)
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	06-Aug-07 (in clinical review)
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	18-May-07 (2), 22-Jun-07
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 30-Jul-07
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 24-Jul-07

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.