

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-780**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**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

NDA 21-780

NAME OF APPLICANT / NDA HOLDER

NOvaDel Pharma, 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)

Pending

ACTIVE INGREDIENT(S)

Nitroglycerin (glycerol trinitrate (GTN))

STRENGTH(S)

0.4 mg.

DOSAGE FORM

lingual spray

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.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**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

5,869,082

b. Issue Date of Patent

2/9/1999

c. Expiration Date of Patent

4/16/2016

d. Name of Patent Owner

NovaDel Pharma Inc.

Address (of Patent Owner)

25 Minneakoning Road

City/State

Flemington / New Jersey

ZIP Code

08822

FAX Number (if available)

908-782-2445

Telephone Number

908-782-3431

E-Mail Address (if available)

gshangold@novadel.com

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)

Gary A. Shangold, MD

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

25 Minneakoning Road

City/State

Flemington / New Jersey

ZIP Code

08822

FAX Number (if available)

908-782-2445

Telephone Number

908-782-3431, Ext. 2201

E-Mail Address (if available)

gshangold@novadel.com

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



6-15-04

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

NovaDel Pharma, Inc.

Address

25 Minneakoning Road

City/State

Flemington / New Jersey

ZIP Code

08822

Telephone Number

908-782-3431

FAX Number (if available)

908-782-2445

E-Mail Address (if available)

gshangold@novadel.com

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.*

**United States Patent** [19]  
**Dugger, III**

[11] Patent Number: **5,869,082**  
 [45] Date of Patent: **Feb. 9, 1999**

[54] **BUCCAL, NON-POLAR SPRAY FOR NITROGLYCERIN**

**FOREIGN PATENT DOCUMENTS**

[75] Inventor: **Harry A. Dugger, III, Flemington, N.J.**

0448961 10/1991 European Pat. Off.  
 2735M74 8/1964 France  
 3246081 6/1984 Germany  
 4038203 6/1992 Germany

[73] Assignee: **Flemington Pharmaceutical Corp., Flemington, N.J.**

*Primary Examiner—Carlos A. Azpuru*  
*Attorney, Agent, or Firm—Omri M. Behr, Esq.*

[21] Appl. No.: **630,064**

[57] **ABSTRACT**

[22] Filed: **Apr. 12, 1996**

A buccal aerosol spray using a non-polar solvent has now been developed which provides nitroglycerin for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal aerosol spray of the invention comprises: propellant 50–95%, non-polar solvent 5–50%, nitroglycerin 0.001–15%, flavoring agent 0.05–5%.

[51] Int. Cl.<sup>6</sup> ..... **A61F 13/02; A61L 9/04**

[52] U.S. Cl. .... **424/435; 424/434; 424/45**

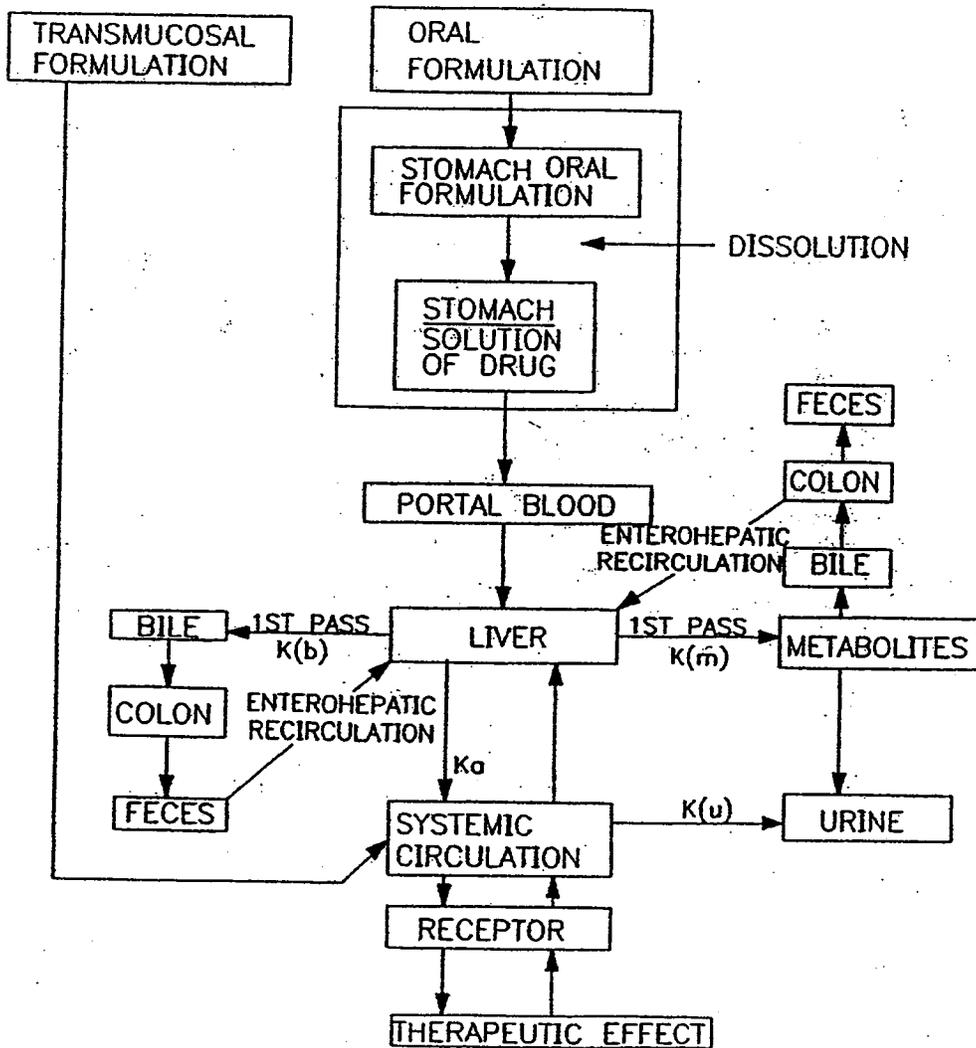
[58] Field of Search ..... **424/434, 435, 424/45**

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

5,428,006 6/1995 Bechgaard et al. .... 514/3

**16 Claims, 1 Drawing Sheet**



$$K(a) = K(m) + K(b) + K(u)$$

## BUCCAL, NON-POLAR SPRAY FOR NITROGLYCERIN

### BACKGROUND OF THE INVENTION

It is known that certain biologically active compounds are better absorbed through the oral mucosa than through other routes of administration, such as through the stomach or intestine. However, formulations suitable for such administration by these latter routes present their own problems. For example, the biologically active compound must be compatible with the other components of the composition such as propellants, solvents, etc. Many such formulations have been proposed. Klokkers-Bethke, describe a nitroglycerin spray for administration to the oral mucosa comprising nitroglycerin, ethanol, and other components. An orally administered pump spray is described by Cholcha in U.S. Pat. No. 5,186,925. Aerosol compositions containing a hydro-carbon propellant and a drug for administration to a mucosal surface are described in U.K. 2,082,457, Su. U.S. Pat. No. 3,155,574, Silson et al. U.S. Pat. No. 5,011,678, Wang et al., and by Parnell in U.S. Pat. No. 5,128,132. It should be noted that these references discuss bioavailability of solutions by inhalation rather than through the membranes to which they are administered.

### SUMMARY OF THE INVENTION

A buccal aerosol spray using a non-polar solvent has now been developed which provides nitroglycerin for rapid absorption through the oral mucosa, resulting in fast onset of effect.

The buccal aerosol spray compositions of the present invention, for transmucosal administration of nitroglycerin soluble in a pharmacologically acceptable non-polar solvent are disclosed comprising in weight % of total composition: pharmaceutically acceptable propellant 50-95%, non-polar solvent 5-50%, nitroglycerin 0.1-6.5%, suitably additionally comprising, by weight of total composition a flavoring agent 0.05-5%. Preferably the composition comprises: propellant 55-85%, non-polar solvent 15-45%, nitroglycerin 0.2-3%, flavoring agent 0.1-2.5%; most suitably propellant 60-80%, non-polar solvent 19-32%, nitroglycerin 0.3-1.5%, flavoring agent 1-2%.

It is an object of the invention to coat the mucosal membranes with extremely fine droplets of spray containing the nitroglycerin.

It is also an object of the invention to administer to a mammal in need of same preferably man, a predetermined amount of nitroglycerin by this method.

A further object is a sealed aerosol spray container containing a composition of the spray formulation, and a metered valve suitable for releasing from said container a predetermined amount of said composition.

As the propellant evaporates after activation of the aerosol valve, a mist of fine droplets is formed which contains solvent and nitroglycerin.

The propellant is a non-Freon material, preferably a C<sub>3-8</sub> hydrocarbon of a linear or branched configuration. The propellant should be substantially non-aqueous. The propellant produces a pressure in the aerosol container such that under expected normal usage it will produce sufficient pressure to expel the solvent from the container when the valve is activated but not excessive pressure such as to damage the container or valve seals.

The solvent is a non-polar hydrocarbon, preferably a C<sub>7-18</sub> hydrocarbon of a linear or branched configuration, its alcohols, and esters thereof, as well as triglycerides, such as miglyol. The solvent must dissolve the nitroglycerin and be miscible with the propellant, i.e., solvent and propellant must form a single phase at 0°-40° C. at a pressure range of 1-3 atm.

The spray compositions of the invention are intended to be administered from a sealed, pressurized container. Unlike a pump spray, which allows the entry of air into the container after every activation, the aerosol container of the invention is sealed at the time of manufacture. The contents of the container are released by activation of a metered valve, which does not allow entry of atmospheric gases with each activation. Such containers are commercially available.

### BRIEF DESCRIPTION OF THE DRAWING

The FIGURE is a schematic diagram showing routes of absorption and processing of pharmacologically active substances in a mammalian system.

### DESCRIPTION OF THE PREFERRED EMBODIMENTS

Nitroglycerin is soluble in the non-polar solvents of the invention at useful concentrations. These concentrations may be less than the standard accepted dose for this compounds since there is enhanced absorption of the compounds through the oral mucosa. This aspect of the invention is especially important because there is a large (40-99.99%) first pass effect.

As propellants for the sprays, propane, N-butane, isobutane, N-pentane, iso-pentane, and neo-pentane, and mixtures thereof may be used. N-butane and iso-butane, as single gases, are the preferred propellants. It is permissible for the propellant to have a water content of no more than 0.2%, typically 0.1-0.2%. (All percentages herein are by weight unless otherwise indicated.) It is also preferable that the propellant be synthetically produced to minimize the presence of contaminants which are harmful to the nitroglycerin. These contaminants include oxidizing agents, reducing agents, Lewis acids or bases, and water. The concentration of each of these should be less than 0.1% except that water may be as high as 0.2%.

The solvent may be selected from the group consisting of C<sub>7-18</sub> hydrocarbons of a linear or branched configuration, the alcohols thereof, the C<sub>2-6</sub> alkanoyl esters and triglycerides of C<sub>7-18</sub> carboxylic acids of a linear or branched configuration.

The preferred flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, sweeteners (sugars, aspartame, saccharin, etc.), and combinations thereof.

While certain formulations are set forth herein, the actual amounts to be administered to the mammal or man in need of same are to be determined by the treating physician.

The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting.

### EXAMPLE 1

#### Nitroglycerin Spray

A spray of the invention comprises the following formulation:

UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION

PATENT NO. : 5,869,082  
DATED : February 9, 1999  
INVENTOR(S) : Harry A. Dugger, III

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,  
Line 1, insert -- non-Freon -- before "propellant".



Attest:

*Brenda Moore*

Attesting Officer

Signed and Sealed this

Fifteenth Day of October, 2002

A handwritten signature in black ink, appearing to read "James E. Rogan", written over a horizontal line.

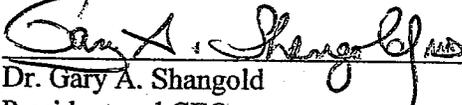
JAMES E. ROGAN  
Director of the United States Patent and Trademark Office

**PATENT CERTIFICATION**

**Paragraph IV Certification**

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, Patent Certification is herein provided for NovaDel Pharma Inc.'s New Drug Application No. ~~21-730~~ for Nitroglycerin Lingual Spray, ~~400~~ mcg per spray.

NovaDel Pharma Inc. ("NovaDel") herein certifies that, in its opinion and to the best of its knowledge, no valid and enforceable claim of U.S. Patent No. 5,186,925 held by G. Pohl-Boskamp GmbH & Co., which expires on February 16, 2010, will be infringed upon by the manufacture, use, sale or offer for sale by NovaDel of Nitroglycerin Lingual Spray, ~~400~~ mcg per spray, for which this application is submitted. This certification is made in accordance with Section 505(b)(2)(A)(iv) of the Federal Food, Drug, and Cosmetic Act and 21 CFR § 314.54(a)(1)(vi). NovaDel further certifies that notice in accordance with Section 505(b)(3)(A) of the Federal Food, Drug, and Cosmetic Act is being provided contemporaneously herewith.

  
\_\_\_\_\_  
Dr. Gary A. Shangold  
President and CEO  
NovaDel Pharma Inc.

\_\_\_\_\_  
Date 6-16-04

**Patent and Exclusivity Search Results from query on Appl No 018705 Product 002 in the OB\_Rx list.**

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**Patent Data**

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
018705	002	5186925	FEB 16,2010			

**Exclusivity Data****There is no unexpired exclusivity for this product.**

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## Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(c)(3)(5).
  2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
  3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
  4. \*PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with \*PED as was done prior to August 18, 2003. Patents with \*PED added after August 18, 2003 will not contain any information relative to the patent itself other than the \*PED extension. Information related specifically to the patent will be conveyed on the original patent only.
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[View a list of all patent use codes](#)[View a list of all exclusivity codes](#)[Return to Electronic Orange Book Home Page](#)

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FDA/Center for Drug Evaluation and Research  
Office of Generic Drugs  
Division of Labeling and Program Support  
Update Frequency:

Orange Book Data - **Monthly**

Orange Book Data Updated Through May, 2004

Orange Book Patent Data Only - **Daily**

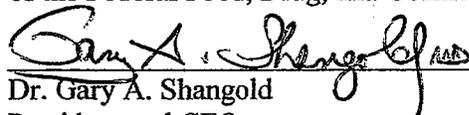
Patent Data Last Updated: July 16, 2004

**PATENT CERTIFICATION**

**Paragraph IV Certification**

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, Patent Certification is herein provided for NovaDel Pharma Inc.'s New Drug Application No. ~~21-780~~ for Nitroglycerin Lingual Spray, ~~400~~ mcg per spray.

NovaDel Pharma Inc. ("NovaDel") herein certifies that, in its opinion and to the best of its knowledge, no valid and enforceable claim of U.S. Patent No. 5,186,925 held by G. Pohl-Boskamp GmbH & Co., which expires on February 16, 2010, will be infringed upon by the manufacture, use, sale or offer for sale by NovaDel of Nitroglycerin Lingual Spray, ~~400~~ mcg per spray, for which this application is submitted. This certification is made in accordance with Section 505(b)(2)(A)(iv) of the Federal Food, Drug, and Cosmetic Act and 21 CFR § 314.54(a)(1)(vi). NovaDel further certifies that notice in accordance with Section 505(b)(3)(A) of the Federal Food, Drug, and Cosmetic Act is being provided contemporaneously herewith.

  
\_\_\_\_\_

Dr. Gary A. Shangold  
President and CEO  
NovaDel Pharma Inc.

\_\_\_\_\_ 6-16-04  
Date

## EXCLUSIVITY SUMMARY

NDA # 21-780

SUPPL # N/A

HFD # 110

Trade Name NitroMist™

Generic Name nitroglycerin lingual aerosol 400 mcg/actuation

Applicant Name NovaDel Pharma Inc.

Approval Date, If Known 11/2/06

### 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?

3 years

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?

no

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.

NOT APPLICABLE

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).

NDA#

NDA#

NDA#

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

(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:

NovaDel Pharma Inc. conducted a single center, placebo-controlled, double-blind, randomized, 4-way, crossover study (FPC 99-033) of nitroglycerin spray using butane as a propellant (instead of CFC) in 30 patients with chronic stable angina pectoris and coronary artery disease to support approval of their 505 (b)(2) application.

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"):

NovaDel Pharma Inc. conducted a single center, placebo-controlled, double-blind, randomized, 4-way, crossover study (FPC 99-033) of nitroglycerin spray using butane as a propellant (instead of CFC) in 30 patients with chronic stable angina pectoris and coronary artery disease to support approval of their 505 (b)(2) application.

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 # 64,596      YES       ! NO   
! Explain:

Investigation #2  
IND #              YES       ! NO   
! Explain:

(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

NOT APPLICABLE

YES

!  
! NO

Explain:

! Explain:

Investigation #2

!

YES

!  
! NO

Explain:

! Explain:

(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: John David

Title: Regulatory Health Project Manager

Date: November 2, 2006

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.

Title: Director, Division of Cardiovascular and Renal Products

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

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/s/

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Norman Stockbridge  
11/6/2006 06:49:54 AM

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## PEDIATRIC PAGE

NDA/BLA #: 21-780 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: June 17, 2004 Action Date: June 17, 2004

HFD- 110 Trade and generic names/dosage form: Nitroglycerin Lingual Spray

Applicant: NovaDel Pharma Therapeutic Class:

Indication(s) previously approved:

Each approved indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: for acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease

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:

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:

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:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*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}*

\_\_\_\_\_  
John David  
Regulatory Project Manager

cc: NDA 21-780  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 12-22-03)

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/s/

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John David

7/13/04 01:08:58 PM

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# NOVADEL PHARMA, INC.

NOVEL DELIVERY OF PHARMACEUTICALS

25 MINNEAKONING ROAD

SUITE 101

FLEMINGTON, NJ 08822

PHONE: 908-782-343, FAX: 908-782-2445

## DEBARMENT CERTIFICATION

I, Jean W. Frydman, of NovaDel Pharma Inc., in my capacity as Vice President and General Counsel, certify in accordance with the requirements of the Generic Drug Enforcement Act of 1992 (Pub. L. No. 102-282, 306 (k), 106 Stat. 149, 158) that NovaDel Pharma, Inc. in connection with NDA 21-780, has not, and will not use in any capacity, the services of any person (including a corporation, partnership, association or individual), who has been debarred from submitting or assisting in the submission of a drug application to the Food and Drug Administration by the Secretary of Health and Human Services, pursuant to Authority conferred to the Secretary, under section 306 (a), and section 306 (b), 106 Stat. 149, 150-152 (1992).

Signature: \_\_\_\_\_

*Jean W. Frydman*

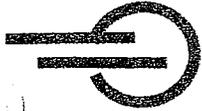
Title: \_\_\_\_\_

*Vice President and General Counsel*

Date: \_\_\_\_\_

*June 24, 2004*

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# NOVADEL PHARMA, INC.

NOVEL DELIVERY OF PHARMACEUTICALS

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SUITE 101

FLEMINGTON, NJ 08822

PHONE: 908-782-343, FAX: 908-782-2445

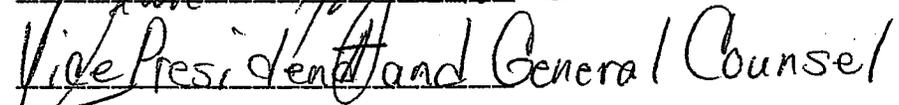
## DEBARMENT CERTIFICATION

I, [Name], of NovaDel Pharma Inc., in my capacity as [Title], certify in accordance with the requirements of the Generic Drug Enforcement Act of 1992 (Pub. L. No. 102-282, 306 (k), 106 Stat. 149, 158) that NovaDel Pharma, Inc. in connection with NDA 21-780, has not, and will not use in any capacity, the services of any person (including a corporation, partnership, association or individual), who has been debarred from submitting or assisting in the submission of a drug application to the Food and Drug Administration by the Secretary of Health and Human Services, pursuant to Authority conferred to the Secretary, under section 306 (a), and section 306 (b), 106 Stat. 149, 150-152 (1992).

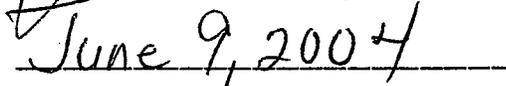
Signature:



Title:



Date:



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**CERTIFICATION: FINANCIAL INTERESTS AND  
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

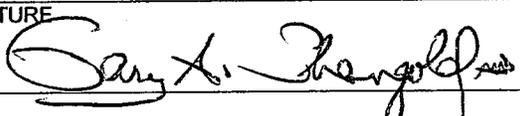
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the 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	_____	

- (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 Gary A. Shangold, M.D.	TITLE President & CEO
FIRM / ORGANIZATION NovaDel Pharma Inc., 25 Mineakoning Road, Flemington, New Jersey 08822	
SIGNATURE 	DATE 7-14-04

**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

# DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning \_\_\_\_\_, who participated as a clinical investigator in the submitted study "Placebo-Controlled, Double-Blind Study of \_\_\_\_\_ Nitroglycerin Spray Using Butane as a Propellant", is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

*Name of clinical investigator*

*Name of*

*clinical study*

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME _____	TITLE Primary Investigator
FIRM / ORGANIZATION _____	
SIGNATURE _____	DATE 26.03.04

### 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 4 hours 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:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

## Memo to the File

Date: October 30, 2006

To: John David  
Regulatory Project Manager, Division of Cardiovascular and Renal  
Products (DCRP)

Subject: Established Pharmacologic Classification for the Highlights of Labeling  
NDA 21-780 (Nitromist™)

This memo provides guidance to the NitroMist review team on how to address the pharmacologic classification requirement [21 CFR 201.57(a)(6)] for the Highlights of labeling.

### Established Pharmacologic Classification of Nitromist:

Although the Office of New Drugs has determined that establishing pharmacologic classification is optimally accomplished with consideration of drugs on a class-by-class basis rather than on a drug-by-drug basis as new labeling is reviewed, we have inadequate time to invoke that process for Nitromist. Additionally, the pharmacologic classification for Nitromist (nitroglycerin lingual spray) is well established in clinical practice. Thus, we propose the following pharmacologic classification to be included in Highlights under the Indications and Usage subheading:

“Nitromist is a **nitrate vasodilator** indicated for.....”

The chemical structure for Nitromist (nitroglycerin) is 1,2,3-propanetriol trinitrate. Nitroglycerin is a **nitrate** compound and in a class of drugs [e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin (oral, intravenous, topical, and transdermal)] that forms free radical nitric oxide (NO). NO activates guanylate cyclase, resulting in an increase of guanosine 3'5' monophosphate (cyclic GMP) in smooth muscle and other tissues. This results in the dephosphorylation of myosin light chains, which regulates the contractile state in smooth muscle. This interaction (**vasodilation**) results in relaxation of the vascular smooth muscle and consequent dilation of peripheral arteries, veins, and coronary arteries. **Venous dilation** promotes decreased venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). **Arteriolar dilation** reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Thus, the term **nitrate vasodilator** provides information on the chemical nature and physiologic effect to adequately describe the pharmacologic classification of Nitromist.

In addition, the term **nitrate** is widely used in the medical community, including resources such as Drug Facts and Comparisons, Drug Information Handbook, Goodman and Gilman's: The Pharmacological Basis of Therapeutics, FDA approved labeling, and PubMed articles. In addition, when identifying class drug interactions (e.g., with PDE5 inhibitors and other vasodilators), this class of drugs are commonly referred to as “nitrates”. The term **nitrate vasodilator** is thus considered scientifically valid and clinically meaningful for the description of the nitroglycerin component of Nitromist.

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/s/  
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William Pierce  
10/30/2006 04:11:27 PM  
INTERDISCIPLINARY

Lilliam Rosario  
10/31/2006 03:54:11 PM  
PHARMACOLOGIST

Laurie Burke  
10/31/2006 04:34:46 PM  
INTERDISCIPLINARY

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# MEMORANDUM

**To:** John David  
Division of Cardiovascular and Renal Products

**From:** Iris Masucci, PharmD, BCPS  
for Study Endpoints and Label Development (SEALD) Team, OND

**Date:** October 29, 2006

**Re:** Comments on draft labeling for NitroMist (nitroglycerin) lingual aerosol  
NDA 21-780

---

We have reviewed the proposed label for NitroMist (sponsor's revised version dated 10-27-06) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

## HIGHLIGHTS

- There is an extra hard return after "Initial U.S. Approval" that should be deleted.

## Indications and Usage

- This section must be in 8-point font as are the rest of the Highlights. The revised version has the indication sentence in 10-point font.
- If you have not already received a consult on the pharmacological classification from the SEALD team, please contact Bill Pierce of SEALD as soon as possible.

## Dosage and Administration

- The intent of Highlights is to make the information as easily accessible as possible using bullets, tables, etc. whenever possible. The current Dosage and Administration section is written as a long paragraph. We suggest it be reworded and presented in a bulleted format for ease of reading. There is also some redundant language about using a maximum of three sprays that can be streamlined.

6 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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/s/

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Iris Masucci  
11/7/2006 10:30:58 AM  
DDMAC REVIEWER

Laurie Burke  
11/7/2006 12:29:16 PM  
INTERDISCIPLINARY

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**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUG QUALITY ASSESSMENT

**DATE:** October 26, 2006

**TO:** Administrative File

**FROM:** Scott N. Goldie, Ph.D.  
Regulatory Health Project Manager for Quality  
Division of Pre-Marketing Assessment I

**SUBJECT:** **Overall Compliance Recommendation**  
NDA 21-780, NitroMist (nitroglycerin lingual spray 0.4mg/mL)

The CDER Office of Compliance (OC) issued an overall 'Acceptable' recommendation for NDA 21-780 on October 24 2006. A copy of the establishment evaluation report is attached.

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

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/s/

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Scott Goldie  
10/26/2006 06:05:44 PM  
PROJECT MANAGER FOR QUALITY

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## ACTION PACKAGE CHECKLIST

Application Information		
BLA # N/A NDA # 21-780	BLA STN# N/A NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A
Proprietary Name: NitroMist™ Established Name: Nitroglycerin Lingual Aerosol Dosage Form: Nitroglycerin Lingual Aerosol		Applicant: NovaDel Pharma Inc.
RPM: John David		Division: Division of Cardiovascular and Renal Products Phone # 301-796-1059
<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 18-705 Pohl-Boskamp, Nitrolingual Pumpspray</p> <p>Provide a brief explanation of how this product is different from the listed drug. Lingual Aerosol , not a Pumpspray</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>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.</b></p> <p><input checked="" type="checkbox"/> Confirmed      <input type="checkbox"/> Corrected Date:</p>	
<p>❖ User Fee Goal Date</p> <p>❖ Action Goal Date (if different)</p>		November 3, 2006
<p>❖ Actions</p> <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<p><input checked="" type="checkbox"/> AP    <input type="checkbox"/> TA    <input type="checkbox"/> AE <input type="checkbox"/> NA    <input type="checkbox"/> CR</p> <p><input type="checkbox"/> None Approvable May 23, 2005</p>
<p>❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)</p>		<p><input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed</p>

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❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  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  BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <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"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input 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

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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>	
<b>Summary Reviews</b>	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	N/A
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	N/A
<b>Labeling</b>	
❖ Package Insert	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	11/1/06
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	10/30/06
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	5/3/06
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	NDAs 18-705, 20-145, 21-134
❖ Patient Package Insert	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	5/3/06
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	N/A
❖ Medication Guide	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	N/A
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	10/31/06
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	10/31/06
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS 9/18/06, 5/26/05, 8/20/04 <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 9/8/06, 1/28/05, 8/10/04 <input checked="" type="checkbox"/> SEALD 10/16/06 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	Date needed XXXXX
❖ 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"> <li>• Center Director's Exception for Review memo</li> <li>• If AP: OC clearance for approval</li> </ul>	
❖ 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	<input checked="" type="checkbox"/> None
• Outgoing Agency request for post-marketing commitments ( <i>if located elsewhere in package, state where located</i> )	N/A
• Incoming submission documenting commitment	N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	yes
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference ( <i>indicate date; approvals only</i> )	N/A
• Pre-NDA/BLA meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg 11/4/03 CMC 2/3/04
• EOP2 meeting ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	N/A
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
• Date of Meeting	N/A
• 48-hour alert or minutes, if available	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	8/14/06, 5/12/05
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• <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> )	5/12/05
• <input checked="" type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	5/12/05 Chemistry review 1, page 101
• <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	N/A <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout)	Date completed: 10/24/06 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul>	N/A <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<b>Nonclinical Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	10/28/04
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	11/15/04
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Page 22 of the medical review dated 11/15/04.
❖ 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> )	❖ 11/15/04 Clinical review, pages 15-16
❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> )	❖ 11/15/04 Clinical review, page 14 & 50
❖ 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 checked="" type="checkbox"/> None requested
• Clinical Studies [11]	N/A
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      4/15/05
❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      4/15/05

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## 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.

## ACTION PACKAGE CHECKLIST

Application Information		
BLA # N/A NDA # 21-780	BLA STN# N/A NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A
Proprietary Name: NitroMist™ Established Name: Nitroglycerin Lingual Aerosol Dosage Form: Nitroglycerin Lingual Aerosol		Applicant: NovaDel Pharma Inc.
RPM: John David	Division: Division of Cardiovascular and Renal Products	Phone # 301-796-1059
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  (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.)	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)):  NDA 18-705 Pohl-Boskamp, Nitrolingual Pumpspray  Provide a brief explanation of how this product is different from the listed drug. Lingual Aerosol , not a Pumpspray  <input type="checkbox"/> If no listed drug, check here and explain:  <b>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.</b>  <input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 11/1/06	
❖ User Fee Goal Date		November 3, 2006
❖ Action Goal Date (if different)		
❖ 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 type="checkbox"/> None Approvable May 23, 2005
❖ 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

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❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 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	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <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"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<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

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On Original

<p>❖ Exclusivity</p> <ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity?             <ul style="list-style-type: none"> <li>• NDAs/BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> <li>• NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> </ul> </li> </ul>	<p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:</p>
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	
<ul style="list-style-type: none"> <li>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<p><input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> <li>• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> <li>• [505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<p>21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii)    <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews).</i>)</li> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for <b>each</b> paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified</p> <p><input checked="" type="checkbox"/> Yes    <input type="checkbox"/> No</p>

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>	
<b>Summary Reviews</b>	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	N/A
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	N/A
<b>Labeling</b>	
❖ Package Insert	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	11/1/06
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	10/30/06
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	5/3/06 NDAs 18-705, 20-145, 21-134
❖ Patient Package Insert	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	5/3/06
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	N/A
❖ Medication Guide	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	N/A
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	10/31/06
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	10/31/06
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS 9/18/06, 5/26/05, 8/20/04 <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 9/8/06, 1/28/05, 8/10/04 <input checked="" type="checkbox"/> SEALD 10/16/06 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	11/2/06, 9/1/04
❖ 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"> <li>Center Director's Exception for Review memo</li> <li>If AP: OC clearance for approval</li> </ul>	N/A
❖ 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"> <li>Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>Incoming submission documenting commitment</li> </ul>	N/A N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	yes
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>EOP2 meeting (<i>indicate date</i>)</li> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	N/A <input type="checkbox"/> No mtg 11/4/03 CMC 2/3/04 <input checked="" type="checkbox"/> No mtg N/A
❖ Advisory Committee Meeting <ul style="list-style-type: none"> <li>Date of Meeting</li> <li>48-hour alert or minutes, if available</li> </ul>	<input checked="" type="checkbox"/> No AC meeting N/A N/A
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	2 <sup>nd</sup> review 8/14/06, 1 <sup>st</sup> review 5/12/05
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <li><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>)</li> <li><input checked="" type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> <li><input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>	5/12/05 5/12/05 Chemistry review 1, page 101 N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	N/A <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection <ul style="list-style-type: none"> <li>NDAs: Facilities inspections (include EER printout)</li> </ul>	Date completed: 10/24/06 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul>	N/A <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<b>Nonclinical Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	10/28/04
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	11/15/04
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Page 22 of the medical review dated 11/15/04.
❖ 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> )	❖ 11/15/04 Clinical review, pages 15-16
❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> )	❖ 11/15/04 Clinical review, page 14 & 50
❖ 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 checked="" type="checkbox"/> None requested
• Clinical Studies	N/A
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      4/15/05
❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      4/15/05

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## 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.

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John David

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**RHPM Overview of NDA 21-780**  
**NitroMist™ (Nitroglycerin) Lingual Aerosol 400 mcg/actuation**  
November 6, 2006

**Sponsor:** NovaDel Pharma Inc.  
**Type:** Chemical Type 3 / S  
**Receipt Date:** June 17, 2004  
**User Fee Goal Date:** November 3, 2006  
**AE Letter Issued:** May 31, 2005  
**Resubmission Letter Issued:** Approval/November 2, 2006  
**Draft Labeling:** May 23, 2005 and May 3, 2006

**Background**

The June 17, 2004, NDA submission was considered a 505(b)(2) fee paying human drug application. It was incomplete and was not accepted for consideration for filing because all fees owed for this application were not paid. Subsequently, the Agency acknowledged receipt of the sponsors revised labeling on August 4, 2004. At that time, the application became a non-fee paying 505(b)(2) application, and the receipt date of the revised labeling is considered the new receipt date for this application.

This submission contains a request for approval of the 15 mL (dose size) aerosol bottle of Nitroglycerin lingual spray (0.4 mg/spray). The product labeling is supported by data from published findings and clinical studies conducted by NovaDel Pharma Inc. and from other sources. The active ingredient, strength, dosage form and route of administration are identical to that of NDA 18-705, although the formulations differ in that dehydrogenated alcohol is a component of the NDA 18-705 product, whereas butane is used in this application.

NovaDel Pharma Inc. conducted a single center, placebo-controlled, double-blind, randomized, 4-way, crossover study of nitroglycerin spray using butane as a propellant (instead of CFC) in 30 patients with chronic stable angina pectoris and coronary artery disease to support approval of their 505 (b)(2) application. The oral spray is a form of delivery modality that has been in use for more than 20 years. This modality provides greater stability compared to the sublingual tablets because the spray is a lipid solution in a metal container that is administered by metered dose. In contrast, repeated opening of a bottle of sublingual nitroglycerin tablets predisposes to chemical breakdown of glyceryl trinitrate to less active compounds by exposure to heat, light, and moisture.

The primary objective of this study was to assess the anti-anginal efficacy of a new aerosol nitroglycerin lingual spray at 3 dosage levels (0.2, 0.4, 0.8 mg per activation) compared to a placebo lingual spray. The study compared 3 sprays (0.2, 0.4, 0.8 mg per activation) with placebo lingual spray in 30 patients with documented stable angina who were considered to be nitrate responders. The study was completed on 12/13/2002.

The Sponsor received an approvable letter dated May 31, 2005 and they submitted a complete response to the approvable letter on April 28, 2006.

**Medical Review**

In his review dated November 15, 2004, Dr. Williams states that he recommends approval of this lingual spray using butane as the propellant.

Dr. William's review (November 15, 2004) concluded that the data from the NovaDel-sponsored single study suggest that treatment of patients with chronic stable angina with aerosol nitrolingual spray (0.2,0.4,0.8 mg per activation) results in increase time from start of exercise to development of moderate

angina in men (only one female) compared to placebo. The sponsor cannot claim that this happens in females based on one female and based on NovaDel-sponsored trial. Furthermore, aerosol nitrolingual spray (0.2,0.4,0.8 mg per activation), in a dose dependent manner, results in increased time to first onset of angina and in time to 1 mm ST segment depression suggesting an anti-anginal affect based on an anti-ischemic effect. At rest, the expected dose related nitrate effects on heart rates and blood pressure were observed. The ability of subjects to exercise to a higher rate-pressure product provides further support for efficacy. The spray was well tolerated based on the relative ratio- frequencies (RRF) of common adverse events and the relative lack of serious adverse events.

He noted that all subjects were Caucasians suggesting that there were no blacks or other ethnic groups in this study. This is against the regulation that other races should be included in studies. The sponsor should not be permitted to use data from other studies since the propellant in other studies is different from butane.

Labeling recommendations were attached to the medical review dated November 15, 2004.

There are no additional mandatory phase 4 studies for this NDA

Financial Disclosure is not applicable as noted on page 22 of the medical review dated November 15, 2004.

#### **Pharmacology Review**

In his review, Dr. Tesfamariam recommended an approvable action and recommended labeling updates based on a recent review of the literature, from the perspective of pharmacology/toxicology. Preclinical and clinical information are extensively cross-referenced.

There were no new preclinical tests submitted as part of this NDA.

#### **Biopharmaceutical Review**

In her review, Dr. Velazquez states the Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-780 and finds the clinical pharmacology and biopharmaceutics section acceptable.

Labeling recommendations are noted in the biopharmaceutical review on pages 3-7.

#### **Chemistry Review**

In his reviews, Dr. Zimmerman states that the chemistry and microbiology data are unacceptable and he recommends that the NDA not be approved from the Chemistry, Manufacturing and Controls perspective. He wrote there are certain critical control aspects that are cited in the draft letter section referenced in the Table of Contents section for 'Draft Deficiency Issues'. These issues include topics relating to

and issues. One critical issue is that the applicant intends to

There is, however, no understanding if this can be completed and validated in a timely manner.

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The sponsor's claim for categorical exclusion from the Environmental Assessment is satisfactory.

Based on the May 3, 2006 resubmission Dr. Shiromani concluded in his chemistry review that this application is recommended for approval from CMC perspective pending satisfactory recommendations from the Office of Compliance for Facilities.

He noted that the following \_\_\_\_\_ comments should be included in the approval action letter:

**Statistical Review**

In his review, Dr. Bai agrees with the sponsor that the data in the study supports the GTN-S's efficacy as a treatment in patients who had angina pectoris due to CAD. However, he noticed that the enrolled patients included all but one subject was female and all subjects were Caucasians. Therefore, generalizability of this result to the entire population of patients cannot be assessed statistically. It should be a clinical judgment.

**Pediatric Rule**

There is no need for pediatric studies as coronary artery disease is predominantly experienced in adults therefore, the Sponsor received a full waiver from conducting studies in the pediatric population in a letter dated July 14, 2004.

**Labeling:**

The sponsor submitted the most recent draft labeling, revised carton and container labels on November 1, 2006.

This NDA will be approved with our draft updated labeling attached to the approval letter.

**Advisory Committee Meeting**

This application did not go before the Advisory Committee.

**Project Manager's Summary**

To my knowledge, there are no issues that might prevent taking regulatory action on this NDA. I submitted an approval on enclosed draft labeling letter for Dr. Stockbridge's signature.

John David, BSN, MS in HRM  
Regulatory Health Project Manager

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**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY**  
**(WO: 22, Mailstop 4447)**

<b>DATE RECEIVED:</b> August 7, 2006	<b>DESIRED COMPLETION DATE:</b> September 7, 2006	<b>OSE REVIEW #:</b> 04-0235-2
<b>DATE OF DOCUMENT:</b> May 3, 2005 & July 7, 2006	<b>PDUFA DATE:</b> November 3, 2006	

**TO:** Norman Stockbridge, M.D.  
Director, Division of Cardiovascular and Renal Products  
HFD-110

**THROUGH:** Nora Roselle, PharmD., Team Leader  
Denise Toyer, PharmD., Deputy Director  
Carol Holquist, RPh., Director  
Division of Medication Errors and Technical Support, HFD-420

**FROM:** Linda M. Wisniewski, RN, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**PRODUCT NAME:** NitroMist  
(Nitroglycerin Lingual Aerosol)  
400 mcg/spray

**NDA# :** 21-780

**DA SPONSOR:** NovaDel Pharma Inc.

**RECOMMENDATIONS:**

DMETS recommends implementation of the label and labeling revisions outlined in section II of this review in order to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

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**Division of Medication Errors and Technical Support (DMETS)**  
**Office of Surveillance and Epidemiology**  
**WO: 22; Mailstop: 4447**  
**Center for Drug Evaluation and Research**

**LABEL AND LABELING REVIEW**

**DATE OF REVIEW:** August 16, 2006

**NDA#:** 21-780

**NAME OF DRUG:** NitroMist  
(Nitroglycerin Lingual Aerosol)  
400 mcg/spray

**NDA HOLDER:** NovaDel Pharma Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Cardiovascular and Renal Products (HFD-110), for assessment of the revised labels and labeling for NitroMist. DMETS previously reviewed the proposed proprietary name, Nitro Mist in ODS Consult #'s 04-0235 (December 10, 2004) and 04-0235-1 (May 26, 2005) and it was found acceptable in both reviews. DMETS also provided label and labeling comments at that time. For this review the sponsor has submitted the presentation of the name to be NitroMist as one word on the container label and carton and insert labeling. Additionally, DMETS notes that the Division has not submitted a request for the final review of the name NitroMist. For this review, the sponsor submitted revised labels and labeling for review and comment.

**PRODUCT INFORMATION**

NitroMist (Nitroglycerin Lingual Aerosol) is a metered-dose spray containing nitroglycerin. NitroMist is indicated for acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease. The usual dose of NitroMist is one or two metered sprays at the onset of an attack. A spray may be repeated approximately every five minutes as needed. No more than three metered sprays are recommended within a 15-minute period. NitroMist may be used prophylactically 5-10 minutes prior to engaging in activities which might precipitate an acute attack. NitroMist is supplied in glass bottles coated with red/orange transparent plastic which assists in containing the glass and medication should the bottle be shattered. Each unit contains 8.5 g of nitroglycerin lingual aerosol and will deliver 230 metered sprays containing 400 micrograms of nitroglycerin per actuation.

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## II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of NitroMist, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following additional areas of improvement, which might minimize potential user error.

### A. GENERAL COMMENTS

1. DMETS does not recommend the use of two different shades of blue in the proprietary name because it distorts the presentation of the proprietary name and provides an unintended emphasis on one section of the name. Revise so that the entire name appears in the same font, color, and prominence.
2. Decrease the prominence of the delivered dose quantity (230 metered doses) statement so that it is less prominent than the strength. Revise the statement '230 metered doses' to read 'Each can delivers approximately 230 metered sprays'. Using the term sprays instead of doses maintains consistency throughout the labels and labeling.

### B. CONTAINER LABEL

1. See GENERAL COMMENTS A1 and A2.
2. The white font on the orange background is difficult to read. Revise the font color to provide for greater readability. Additionally, we note that there are portions of the label that are presented in all capital letters. This is difficult to read and the important information is hard to decipher from the less important information. Revise to include the use of title case letters versus all capital letters to improve readability.
3. We note that in the current presentation, the dot of the letter 'i' is presented as a graphic of spray. Revise so that the dot is presented in the same font and color as the rest of the name as recommended in General Comment #1.
4. Relocate the strength so that it appears directly below the established name. There should be no interfering matter (i.e. blue line) between the drug name and strength. We refer you to 21 CFR 201.10(a). The strength should appear in the box that contains the proprietary and established name and be located directly under the established name. For example:

NitroMist  
(Nitroglycerin Lingual Aerosol)  
400 mcg/spray

5. Revise the word '~~USUAL DOSAGE~~' to read 'Usual Dosage'. Please revise the font to be title case rather than all capital letters.

### C. CARTON LABELING

1. See GENERAL COMMENT A1, B3, and B4.
2. Increase the size of the established name so that it is at least ½ the size of the proprietary name.
3. Relocate the strength so that it is in close proximity to the proprietary and established name. Increase its prominence to be commensurate with the proprietary and established names.
4. Consider revising the word \_\_\_\_\_ as it may not easily be understood by the general public. Use a term that is easily understood by the general public, for example "Do not spit...".
5. Delete the statements \_\_\_\_\_ and \_\_\_\_\_ as they are currently presented on the back and side panels respectively or revise the presentation so that it appears as one phrase "Container should be upright when stored or used".
6. Delete the patent number information from the principal display panel. We recommend relocating the patent number to the back or side panel.
7. Include the statement "As directed by the physician" to the section referring to the prophylactic use of NitroMist prior to engaging in activities that might cause chest pain.
8. Revise the position of the warning statements so that all the patient warnings are listed together and all the storage warnings are together.
9. \_\_\_\_\_
10. The DOSAGE section states to '... \_\_\_\_\_.' This is unclear. Do patients need to take 1 spray then wait 5 minutes and repeat or can they take 2 sprays (800 mcg), at one time, then repeat if necessary?

### D. INSERT LABELING

1. In the DOSAGE AND ADMINISTRATION section, the second and third paragraphs should contain headers labeled \_\_\_\_\_ and \_\_\_\_\_, respectively, in order to direct the user to the appropriate section. The way the information is currently presented, the user may stop reading the Dosage and Administration section at the completion of the first paragraph.
2. Information about priming appears in the first sentence of the second paragraph. This information is not prominent and can be overlooked because it appears in the middle of the Dosage and Administration section. Overlooking the priming information may cause a patient to believe they received medication when in actuality, they did not. It is pertinent that the priming of NitroMist appear prominently at the beginning of the Dosage and Administration section, especially since it must be initially primed with ten sprays, and then reprimed with two sprays after being unused for six weeks.

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Linda Wisniewski  
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
9/18/2006 04:02:03 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
9/18/2006 04:19:41 PM  
DRUG SAFETY OFFICE REVIEWER

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# MEMORANDUM

**To:** John David  
Division of Cardiovascular and Renal Products  
Office of New Drugs

**From:** Lisa Hubbard, R.Ph., Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications

**Date:** September 8, 2006

**Re:** Comments on draft labeling:  
NDA 21-780  
NitroMist™ (Nitroglycerin Lingual Aerosol)

---

DDMAC has reviewed the proposed package insert for NDA 21-780 (nitroglycerin lingual aerosol) and offer the following comments with regard to promotional considerations (Please also see our review dated August 10, 2004.):

## **Contraindications:**

- The approved package insert (PI) for the reference listed drug (RLD) states, "Nitrolingual Pumpspray is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites." However, the proposed package insert for NitroMist states, "NitroMist™ is not contraindicated in patients who are allergic to or idiosyncratic for other nitrates or nitrites." This could be used promotionally to suggest that NitroMist™ is safer because it is not specifically contraindicated for patients who are allergic to or idiosyncratic for other nitrates or nitrites.
- Please consider eliminating the proprietary names of the PDE5 inhibitors from this section of the package insert.

## **Precautions:**

### General

- The fifth paragraph in this section discusses industrial workers and claims that "The RLD PI states that 'the change in wording could be used to suggest that NitroMist™ is safer than the RLD. Please consider using the same language for both products."

## **Adverse Reactions**

- Please consider including a listing of adverse reactions in table format in the label, provided data is available.

## **Dosage and Administration**

- The proposed package insert does not appear to have a federal precautionary "Rx only" statement.

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Lisa Hubbard  
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DDMAC REVIEWER

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# REQUEST FOR CONSULTATION

TO (Division/Office):  
DMETS/ODS, HFD-420

FROM:  
LCDR John David

DATE 8/7/06	IND NO.	NDA NO. 21-780	TYPE OF DOCUMENT DMETS Consult	DATE OF DOCUMENT 8/7/06
NAME OF DRUG Nitroglycerin Lingual Spray LS, 0.4 mg (Aerosol)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Vasodialator	DESIRED COMPLETION DATE 9/7/06

NAME OF FIRM: NovaDel Pharma Inc.

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

### V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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### COMMENTS/SPECIAL INSTRUCTIONS:

Please re-evaluate the attached labeling.

The application goal date is November 3, 2006.

The proposed labeling is in EDR.

Thank you!

SIGNATURE OF REQUESTER CDR John David	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

-----  
John David  
8/7/2006 11:49:33 AM

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On Original**

DICKSTEIN SHAPIRO MORIN & OSHINSKY LLP

2101 L Street NW • Washington, DC 20037-1526

Tel (202) 785-9700 • Fax (202) 887-0689

Writer's Direct Dial: (202) 775-4786

Writer's EMail: [BradyJ@DSMO.com](mailto:BradyJ@DSMO.com)

March 21, 2005

**VIA FEDERAL EXPRESS**

Chief Executive Officer  
G. Pohl Boskamp GmbH & Co.  
Kieler Strausse 11  
D-25551 Hohenlockstedt  
P.O. Box 1253  
Germany

Re: Notice of Paragraph IV Certification  
United States Patent No. 5,186,925  
Nitrolingual® Pumpspray  
(nitroglycerin lingual spray), 400 mcg per spray  
Our Reference: N9810.0053

Dear Sir or Madam:

We represent NovaDel Pharma Inc. ("NovaDel") and, on behalf of NovaDel, hereby provide the following information to G. Pohl Boskamp GmbH & Co. ("Pohl Boskamp") as the holder of NDA 18-705 for Nitrolingual® Pumpspray and owner of United States Patent No. 5,186,925 ("the '925 patent") entitled "Nitroglycerin Pump Spray," pursuant to 21 U.S.C. § 355(b)(3)(D) of the Federal Food, Drug, and Cosmetic Act, 21 C.F.R. § 314.54:

1. NovaDel has submitted to the United States Food and Drug Administration ("FDA") a New Drug Application ("NDA") under 21 U.S.C. § 355(b)(2), which contains the required bioavailability or bioequivalence data and a paragraph IV patent certification, and which seeks approval to engage in the commercial manufacture, use, and sale of nitroglycerin lingual sprays, 400 mcg per spray ("the NovaDel Products") before the expiration of the '925 patent.

2. The NDA for the NovaDel Products was accepted for filing by the FDA on October 4, 2004 and was assigned number 21-780.

1177 Avenue of the Americas • New York, NY 10036-2714

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DSMDB.1899755.2

G. Pohl Boskamp GmbH & Co.

March 21, 2005

Page 2

3. The active ingredient of the NovaDel Products is nitroglycerin; the strength is 400 mcg, and the dosage form is a lingual spray.

4. The current edition of Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") identifies one patent, the '925 patent, that is represented to be related to Nitrolingual® Pumpspray (nitroglycerin lingual spray). See 21 U.S.C. § 355(b)(1). The '925 patent will expire on February 16, 2010. NovaDel, which has applied for approval of the FDA to market certain nitroglycerin lingual sprays prior to expiration of the '925 patent, hereby confirms that no valid and enforceable claim of the '925 patent will be infringed by the manufacture, use, sale, or offer for sale of the NovaDel Products for which the above-referenced NDA has been submitted.

5. A detailed statement of the factual and legal basis for NovaDel's position regarding the '925 patent is set forth below.

**DETAILED FACTUAL AND LEGAL BASIS  
FOR NON-INFRINGEMENT OF UNITED STATES PATENT NO. 5,186,925  
UNDER 21 U.S.C. § 355(b)(3)(D)(ii)**

I. THE '925 PATENT

The '925 patent, entitled "Nitroglycerin Pump Spray," issued on February 16, 1993, based on application Serial No. 665,087, filed March 6, 1991, and claims a priority date of March 10, 1990, based on German patent application No. 4007705. The '925 patent issued with five claims, of which claim 1 is the only independent claim. Independent claim 1 is as follows:

1. Nitroglycerin pump spray containing 0.2 to 3.5% by wt. of nitroglycerin and up to 3% by wt. of additives selected from the group consisting of flavouring agents and antioxidants, and a liquid phase consisting of 10 to 40% by wt. of ethyl alcohol and 90 to 60% by wt. of synthetic or natural fatty oils.

G. Pohl Boskamp GmbH & Co.

March 21, 2005

Page 3

Claim 2 depends from claim 1 and further defines the liquid phase as consisting of 15 to 30% by weight of ethyl alcohol and 85 to 70% by weight of the fatty oils. Claim 3 depends from claim 1 and further defines the liquid phase as consisting of about 20% by weight of ethyl alcohol and about 80% by weight of the fatty oils. Claim 4 depends from claim 1 and further defines the fatty oil as a saturated natural oil or a C<sub>8</sub> to C<sub>12</sub> fatty acid triglyceride. Claim 5 depends from claim 4 and limits the saturated natural oil to rape oil.

II. THE NOVADDEL PRODUCTS DO NOT INFRINGE ANY CLAIM OF THE '925 PATENT EITHER LITERALLY OR UNDER THE DOCTRINE OF EQUIVALENTS

The burden is on the patent owner to establish infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988). To establish infringement, every limitation set forth in a claim must be found in the accused product, either literally or under the doctrine of equivalents. *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995). The first step in an infringement analysis is determining the meaning and scope of the patent claims. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Claim construction is based primarily upon an examination of the intrinsic evidence, i.e., the words of the claims in question, the patent specification, and the prosecution history. *Id.* at 979-80. After arriving at a proper interpretation of the claims, the claims are compared to the accused product to determine whether or not there is infringement. *Id.* at 976. If there is a one-to-one literal correspondence between the words of the claims and the accused product, then there is "literal" infringement. If any limitation of the claim is omitted, then the patent is not literally infringed. See *Overhead Door Corp. v. Chamberlain Group, Inc.*, 194 F.3d 1261, 1269 (Fed. Cir. 1999).

When an accused product does not literally infringe a claim, infringement may nonetheless be found under the doctrine of equivalents. Under the doctrine of equivalents, an accused product may infringe a claim if there are only insubstantial differences between the elements of the claimed invention and the accused product. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997); *Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1309 (Fed. Cir. 2000) ("The usual test of the substantiality of

the differences is whether the element in the accused composition performs substantially the same function in substantially the same way to obtain substantially the same result as the claimed element."). There can be no infringement under the doctrine of equivalents if a claim limitation is totally missing from the accused device. *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1539 (Fed. Cir. 1991). "The doctrine of equivalents is not a license to ignore claim limitations." *Dolly, Inc. v. Spalding & Evenflow Cos.*, 16 F.3d 394, 398 (Fed. Cir. 1994). A "court cannot 'convert a multi-limitation claim to one of [fewer] limitations to support a finding of equivalency.'" *Id.* at 399.

A. The NovaDel Products Do Not Literally Infringe Any Claim Of The '925 Patent

The NovaDel Products do not literally infringe any claim of the '925 patent for at least the following reasons. First, claims 1-5 of the '925 patent are limited to nitroglycerin pump sprays that have a liquid phase "consisting of 10 to 40% by wt. of ethyl alcohol and 90 to 60% by wt. of synthetic or natural fatty oils." (Col. 4, lines 29-31.) The "consisting of" transitional phrase is a closed phrase which excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520 (CCPA 1931); *Mannesmann Demag Corp. v. Engineered Metal Products Co.*, 793 F.2d 1279 (Fed. Cir. 1986). In determining whether a claim is infringed, the phrase "consisting of" limits the claim to that which is expressly set forth in the claim. *See, Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382-83 (Fed. Cir. 2000). Moreover, the applicant argued during the prosecution history of the '925 patent that the claimed invention "includes a liquid phase which only consists of ethyl alcohol and neutral oil...." (Amendment dated October 30, 1991, page 6.)

The NovaDel Products do not infringe any claim of the '925 patent because the NovaDel products contain an additional element. In contrast to claims 1-5 of the '925 patent, the liquid phase of the NovaDel Products contains substantial amounts of a different compound, a propellant. The "consisting of" language limits the claimed liquid phase to the recited ingredients and no other substances; that is, the liquid phase "consists of" only the ethyl alcohol and synthetic or natural fatty oils. Since the liquid phase of the NovaDel Products contains a propellant, which is different from those

G. Pohl Boskamp GmbH & Co.

March 21, 2005

Page 5

substances expressly recited in the claims, the NovaDel Products do not literally infringe any claim of the '925 patent.

Second, the NovaDel Products lack an element required in claims 1-5 of the '925 patent, ethyl alcohol. The NovaDel Products do not contain any amount of ethyl alcohol. Because the NovaDel Products lack ethyl alcohol, a requirement of claims 1-5, there can be no literal infringement as a matter of law. *Overhead Door*, 194 F.3d at 1269.

Third, the preamble of claims 1-5 of the '925 patent recite a "pump spray," which, according to the '925 patent is an "open system" propellant-free spray. (Col. 4, lines 26-31; Col. 1, lines 30-33.) During the prosecution of the application that issued as the '925 patent, the applicant repeatedly characterized the alleged invention as a "pump spray," and distinguished the claims over the cited art, by asserting that the "open system" pump spray of the present invention is "quite different" from a pressurized aerosol ("closed") system. (Response to April 30, 1991 Office Action at 7; Response to February 3, 1992 Office Action at 5.) The applicant further argued that in the practice of the nitroglycerin pump spray composition claimed in the '925 patent, one would not include readily vaporizable substances in the composition as there would exist a great risk that the nitroglycerin concentration would considerably increase due to vaporization of the volatile component leading to an explosive decomposition, thereby creating a potentially dangerous or explosive effect. In cases where, as here, the patentee used the preamble of the claim to define the subject matter of the invention, the preamble is considered necessary to give life, meaning, and vitality to the claims. *See In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994); *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620-21 (Fed. Cir. 1995). Accordingly, claims 1-5 of the '925 patent are limited to "pump sprays," which are properly construed as "open container" systems.

The NovaDel Products are not "pump sprays," i.e., open systems without propellant. In contrast to the claimed pump sprays, the inclusion of readily vaporizable substances in closed systems is not a concern since the substances will not vaporize in the sealed, closed system. The NovaDel Products are closed systems with a pressurized propellant, and therefore fail to meet the "pump spray" requirement of the claims of the '925 patent. Thus, for at least this additional reason, the NovaDel Products do not literally infringe any claim of the '925 patent.

B. The NovaDel Products Do Not Infringe Any Claim Of The '925 Patent Under The Doctrine Of Equivalents

The NovaDel Products do not contain an equivalent to any of the above missing claim limitations. First, with respect to the liquid phase of the claimed nitroglycerin pump spray composition, the term "consisting of" emphasizes the claims' specific limitation to a liquid phase of only ethyl alcohol and a synthetic or natural fatty oil. The NovaDel Products have a liquid phase that contains a substantial amount of a different ingredient, a propellant. Since this is a substantial difference between the claims and the NovaDel Products, there can be no infringement under the doctrine of equivalents. In addition, the doctrine of prosecution history estoppel provides a substantive limitation on the application of the doctrine of equivalents by "preventing recapture of subject matter surrendered during prosecution of the patent." *Southwall Techs.*, 54 F.3d at 1579. During prosecution of the application that led to the issuance of the '925 patent, the applicant distinguished the alleged invention over the cited art by arguing that its claims were directed to a liquid phase that "only consists of ethyl alcohol and neutral oil [later amended to 'fatty oils']" (Amendment dated October 30, 1991, at page 6). It is well settled that "[c]lear assertions made during prosecution in support of patentability" will create an estoppel. *Id.* at 1583. In view of the assertions the applicant made during prosecution, the applicant is estopped from asserting a range of equivalents that would encompass the propellant-containing liquid phase formulation of the NovaDel Products.

Likewise, the NovaDel Products completely lack ethyl alcohol, and fail to contain any element that could remotely be considered an equivalent to the 10-40% ethyl alcohol of claim 1 or the more specific amounts of ethyl alcohol in any of the dependent claims. Moreover, the applicant repeatedly emphasized the amount of ethyl alcohol present in the claimed pump spray during the prosecution history as a basis for distinguishing the prior art and obtaining allowance of the application for the '925 patent. There can be no infringement under the doctrine of equivalents when an element is completely missing, either literally or by any equivalent. Furthermore, under the doctrine of prosecution history estoppel, the patentee is now estopped from asserting a range of equivalents that would cover a formulation that does not contain any ethyl alcohol, much less the specifically claimed amounts of ethyl alcohol.

G. Pohl Boskamp GmbH & Co.

March 21, 2005

Page 7

Finally, NovaDel's Products do not contain any equivalent of the claimed "pump spray." In distinguishing prior art cited by the Examiner, the applicant noted that the prior art "... discloses a closed system gas pressurized aerosol and in no way suggests the presently claimed invention which includes an open system pump spray. [The prior art] clearly relates to a gas pressurized aerosol which has nothing to do at all with a pump spray." (Amendment dated June 26, 1992, at pages 3-4 (emphasis added).) By applicant's own admission, this distinction "is of great importance" and "closed systems" have "nothing to do at all" with the "open system" pump sprays of the alleged invention. (Response to April 30, 1991 Office Action at 6; Response to February 3, 1992 Office Action at 3-6, 8.) Accordingly, the NovaDel Products are substantially different from the '925 patent claims. In addition, as set forth above, the doctrine of prosecution history estoppel provides a substantive limitation on the application of the doctrine of equivalents by "preventing recapture of subject matter surrendered during prosecution of the patent." *Southwall Techs.*, 54 F.3d at 1579. Since the applicant repeatedly distinguished the alleged invention by asserting that its claims were directed to "open system" pump sprays, rather than propellant containing "closed systems," the patentee has disavowed and is now estopped from asserting a range of equivalents that would encompass pressurized propellant-containing closed system formulations of the NovaDel Products.

Accordingly, the NovaDel Products also do not infringe any claim of the '925 patent under the doctrine of equivalents for at least the aforementioned reasons.

### III. CONCLUSION

For at least the foregoing reasons, no claim of the '925 patent will be infringed, either literally or under the doctrine of equivalents, by the manufacture, use, importation, sale, or offer of sale of the NovaDel Products. NovaDel expressly reserves the right to challenge the validity and enforceability of the above patent and/or any assertion of infringement that Pohl Boskamp might make during the course of any ensuing litigation between the parties.

We would be willing to provide certain additional information in confidence, including allowing a sample of the NovaDel Products to be tested in confidence by an independent lab. If you wish to consider such additional information for the purpose of

G. Pohl Boskamp GmbH & Co.

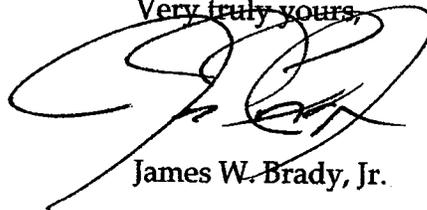
March 21, 2005

Page 8

confirming, as indicated above, that there is no infringement by the NovaDel Products, please let us know and we will send you a suitable confidentiality agreement pursuant to 21 U.S.C. 355(c)(3)(D)(i)(III). If you desire to have the NovaDel Products tested by an independent lab, please let us have the name of the lab and the contact person to whom we should forward a sample.

If you have any questions or comments, please do not hesitate to contact the undersigned.

Very truly yours,

A handwritten signature in black ink, appearing to be "JWB", written over the typed name "James W. Brady, Jr.".

James W. Brady, Jr.

JWB/lja

cc: First Horizon Pharmaceutical Corp.  
Jean W. Frydman, Esq.

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**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
Rockville, MD 20857

Woodmont II  
1451 Rockville Pike  
Rockville, MD 20852

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**Transmitted to FAX Number:** 301-827-5562

**Attention:** Michael Jones

**Company Name:** FDA

**Phone:** 301-443-5532

**Subject:** User fee info r/t 505 (b) (2) application for  
NDA 21-780 Nitroglycerin Lingual Spray

**Date:** July 9, 2004

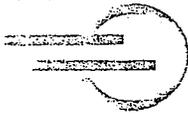
**Pages including this sheet:** 8

**From:** John David, BSN, MS in HRM  
LCDR, U.S. Public Health Service  
Regulatory Health Project Manager

**Phone:** 301-594-5368

**Fax:** 301-594-5494

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**NOVADEL PHARMA INC.**  
NOVEL DELIVERY OF PHARMACEUTICALS

**FAX**

<b>Date:</b>	June 5, 2003
<b>To:</b>	Tawni Schwemer CDER's User Fee Staff
<b>Fax:</b>	301-827-0951
<b>Phone:</b>	301-594-2041
<b>From:</b>	Paul Decker
<b>Phone:</b>	908-782-3431, Ext. 38
<b>Fax:</b>	908-782-2445
<b>Pages:</b>	4 with cover
<b>RE:</b>	User Fee Cover Sheet

Dear Tawni

As per our conversation concerning the fee for our 505(B)(2) submission. I have attached the proposed draft of our labeling for nitroglycerin lingual spray for your review. The NDA we will reference is NDA 18705 "Nitrolingual Spray (nitroglycerin lingual aerosol)".

It is our interpretation of instruction #7 Exclusions (from form FDA 3397) that reads: Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); and NOT a new indication for a use. Our product is not a new molecular entity nor is it for a new indication.

Please note under description our inactive ingredients include n-butane as our propellant in place of the propellant noted in NDA 18705. Also the name of our lingual spray entered on the draft labeling is a place holder only. Other than the results of our own testing and dosage forms the labeling is very similar.

Thank you  
Paul

6-25-03

Tawni

*Returned call + had one question:  
Why are we <sup>not</sup> submitting ANDA rather than NDA?*

301-554-5629

594-

**From:** Schwemer, Tawni B  
**Date:** Wednesday, July 16, 2003 10:13:06 AM  
**To:** 'pdecker@novadel.com'  
**Subject:** NovaLingual Aerospray

Mr. Decker,

Per our earlier conversation today and per your request, I'm sending you an e-mail regarding our conversation.

We have reviewed the labeling that you provided to me, via fax, on June 25, 2003. Based on what we have seen, we do not feel that this will be a fee-paying 505(b)(2) application. Please keep in mind that this decision is based on what we have seen. When you submit your application, the Project Manager will review your labeling again. He will be checking for any differences between what we have seen and what is submitted at that time. If anything changes in your labeling, your application could become a fee-paying 505(b)(2) application.

If you have any further questions, feel free to contact us again.

Thank you,  
Tawni Schwemer  
Policy Analyst  
CDER/Office Regulatory Policy

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**FAX**

<b>Date:</b>	June 5, 2003
<b>To:</b>	Tawni Schwemer CDER's User Fee Staff
<b>Fax:</b>	301-827-0951
<b>Phone:</b>	301-594-2041
<b>From:</b>	Paul Decker
<b>Phone:</b>	908-782-3431, Ext. 38
<b>Fax:</b>	908-782-2445
<b>Pages:</b>	4 with cover
<b>RE:</b>	User Fee Cover Sheet

Dear Tawni

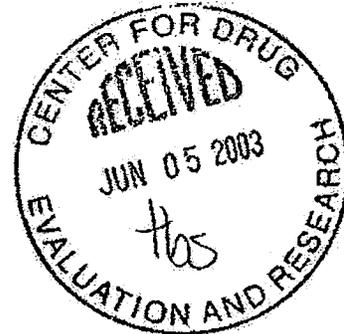
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Please note under description our inactive ingredients include n-butane as our propellant in place of the propellant noted in NDA 18705. Also the name of our lingual spray entered on the draft labeling is a place holder only. Other than the results of our own testing and dosage forms the labeling is very similar.

Thank you  
Paul

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3 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

**RHPM Overview of NDA 21-780**  
**NitroMist™ (Nitroglycerin Lingual Aerosol) 400 mcg/actuation**  
**May 31, 2005**

**Sponsor:** NovaDel Pharma Inc.  
**Type:** Chemical Type 3 / S  
**Receipt Date:** June 17, 2004  
**User Fee Goal Date:** June 4, 2005  
**AE Letter Issued:** May 31, 2005  
**Draft Labeling:** May 23, 2005

**Background**

The June 17, 2004, NDA submission was considered a 505(b)(2) fee paying human drug application. It was incomplete and was not accepted for consideration for filing because all fees owed for this application were not paid. Subsequently, the Agency acknowledged receipt of the sponsors revised labeling on August 4, 2004. At that time, the application became a non-fee paying 505(b)(2) application, and the receipt date of the revised labeling is considered the new receipt date for this application.

This submission contains a request for approval of the 15 mL (—dose size) aerosol bottle of Nitroglycerin lingual spray (0.4 mg/spray). The product labeling is supported by data from published findings and clinical studies conducted by NovaDel Pharma Inc. and from other sources. The active ingredient, strength, dosage form and route of administration are identical to that of NDA 18-705 although the formulations differ in that dehydrogenated alcohol is a component of the NDA 18-705 product, whereas butane is used in this application.

NovaDel Pharma Inc. conducted a single center, placebo-controlled, double-blind, randomized, 4-way, crossover study of nitroglycerin spray using butane as a propellant (instead of CFC) in 30 patients with chronic stable angina pectoris and coronary artery disease to support approval of their 505 (b)(2) application. The oral spray is a form of delivery modality that has been in use for more than 20 years. This modality provides greater stability compared to the sublingual tablets because the spray is a lipid solution in a metal container that is administered by metered dose. In contrast, repeated opening of a bottle of sublingual nitroglycerin tablets predisposes to chemical breakdown of glyceryl trinitrate to less active compounds by exposure to heat, light, and moisture.

The primary objective of this study was to assess the anti-anginal efficacy of a new aerosol nitroglycerin lingual spray at 3 dosage levels (0.2, 0.4, 0.8 mg per activation) compared to a placebo lingual spray. The study compared 3 sprays (0.2, 0.4, 0.8 mg per activation) with placebo lingual spray in 30 patients with documented stable angina who were considered to be nitrate responders. The study was completed on 12/13/2002.

**Medical Review**

In his review dated November 15, 2004, Dr. Williams states that he recommends approval of this lingual spray using butane as the propellant.

Dr. William's review (November 15, 2004) concluded that the data from the NovaDel-sponsored single study suggest that treatment of patients with chronic stable angina with aerosol nitrolingual spray (0.2,0.4,0.8 mg per activation) results in increase time from start of exercise to development of moderate angina in men (only one female) compared to placebo. The sponsor cannot claim that this happens in females based on one female and based on NovaDel-sponsored trial. Furthermore, aerosol nitrolingual spray (0.2,0.4,0.8 mg per activation), in a dose dependent manner, results in increased time to first onset of angina and in time to 1 mm ST segment depression suggesting an anti-anginal affect based on an anti-ischemic effect. At rest, the expected dose related nitrate effects on heart rates and blood pressure were observed. The ability of subjects to exercise to a higher rate-pressure product provides further support for

efficacy. The spray was well tolerated based on the relative ratio- frequencies (RRF) of common adverse events and the relative lack of serious adverse events.

He noted that all subjects were Caucasians suggesting that there were no blacks or other ethnic groups in this study. This is against the regulation that other races should be included in studies. The sponsor should not be permitted to use data from other studies since the propellant in other studies is different from butane.

Labeling recommendations were attached to the medical review dated November 15, 2004.

There are no additional mandatory phase 4 studies for this NDA.

Financial Disclosure is not applicable as noted on page 22 of the medical review dated November 15, 2004.

#### **Pharmacology Review**

In his review, Dr. Tesfamariam recommended an approvable action and recommended labeling updates based on a recent review of the literature, from the perspective of pharmacology/toxicology. Preclinical and clinical information are extensively cross-referenced.

There were no new preclinical tests submitted as part of this NDA.

#### **Biopharmaceutical Review**

In her review, Dr. Velazquez states the Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-780 and finds the clinical pharmacology and biopharmaceutics section acceptable.

Labeling recommendations are noted in the biopharmaceutical review on pages 3-7.

#### **Chemistry Review**

In his reviews, Dr. Zimmerman states that the chemistry and microbiology data are unacceptable and he recommends that the NDA not be approved from the Chemistry, Manufacturing and Controls perspective. He wrote there are certain critical control aspects that are cited in the draft letter section referenced in the Table of Contents section for 'Draft Deficiency Issues'. These issues include topics relating to

issues. One critical issue is that the applicant intends to revise there

there is, however, no understanding if this can be completed and validated in a timely manner.

The sponsor's claim for categorical exclusion from the Environmental Assessment is satisfactory.

**Statistical Review**

In his review, Dr. Bai agrees with the sponsor that the data in the study supports the GTN-S's efficacy as a treatment in patients who had angina pectoris due to CAD. However, he noticed that the enrolled patients included all but one subject was female and all subjects were Caucasians. Therefore, generalizability of this result to the entire population of patients cannot be assessed statistically. It should be a clinical judgment.

**Pediatric Rule**

There is no need for pediatric studies as coronary artery disease is predominantly experienced in adults therefore, the Sponsor received a full waiver from conducting studies in the pediatric population in a letter dated July 14, 2004.

**Labeling:**

The sponsor submitted the most recent draft labeling on May 23, 2005 and plans to submit the revised carton and container labels prior to May 31, 2005.

This NDA will be approvable with our draft updated labeling attached to the approvable letter.

**Advisory Committee Meeting**

This application did not go before the Advisory Committee.

**Project Manager's Summary**

To my knowledge, there are no issues that might prevent taking regulatory action on this NDA. I will submit an approvable letter for Dr. Stockbridge's signature.

John David, BSN, MS in HRM  
Regulatory Health Project Manager

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

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John David  
6/3/05 09:17:02 AM  
CSO

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