NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-780	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: NitroMist™, (Nitroglycerin Lingual Aerosol) 400 mcg/actuation		Applicant: NovaDel Pharma Inc.	
RPM: John David		HFD- 110	Phone # 301-594-5309

Application Type: ( ) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (X) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 18-705 Pohl-Boskamp, Nitrolingual Pumpspray

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	June 4, 2005
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number See below
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation (X) Other (specify) See below
• User Fee exception	( ) Orphan designation (X) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	( ) Verified
• 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.	21 CFR 314.50(i)(1)(*i*)(A) (X) Verified (paragraph IV certification to NDA 18-705) 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III 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).	N/A
• [505(b)(2) applications] For each paragraph IV 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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) (X) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's 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)? *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 box below (Exclusivity).* *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?	(X) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)? *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 box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes (X) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the 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 within the 45-day period). *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 box below (Exclusivity).* *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.*	( ) Yes (X) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *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.*	N/A ( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Project Manager 5/31/05

General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA (X) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	5/11/05
• Most recent applicant-proposed labeling	5/16/05
• Original applicant-proposed labeling	8/4/04
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC 1/28/05 DMETS 8/20/04 DDMAC 8/10/04 DMETS 5/26/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NDA 18-705 NDA 20-145 NDA 21-134
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	5/18/05
• Applicant proposed	8/6/05, 5/15/05, 5/23/05
• Reviews	DDMAC 1/28/05 DMETS 8/20/04 DDMAC 8/10/04 DMETS 5/26/05
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Enclosed
❖ Memoranda and Telecons	Enclosed
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	11/4/03 CMC 2/3/04
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

/s/

John David
6/3/05 09:06:06 AM

Appears This Way
On Original

NovaDel Pharma, Inc.
Novel Delivery of Pharmaceuticals

Norman Stockbridge, MD, Ph.D.
Director of Division of Cardio-Renal Drug Products
CDER - Office of Drug Evaluation I (HFD-110)
Food and Drug Administration (FDA)
5600 Fishers Lane
Rockville, MD 20857

Attention: Comdr. John David

cc. Jean Frydman, NovaDel Pharma Inc.
Vice President & General Counsel

Re: NDA 21-780 Nitroglycerin Lingual Aerosol, 400 mcg./actuation

Subject: Amendment 20 – Patent Certification Paragraph IV - Notification Status

Dear Dr. Stockbridge:

Be advised that as of this date, NovaDel Pharma Inc. has not been notified by either First Horizon Pharmaceutical Corporation or Pohl Boskamp GmbH & Co. contesting the "no patent infringement" filing status of NDA 21-780 Patent Certification under Paragraph IV submitted to FDA as Amendment 16 on 24th March 2005.

First Horizon Pharmaceutical Corporation – notification receipt date is 22nd March 2005
Phol Boskamp GmbH & Co. – notification receipt date is 23rd March 2005

This submission includes:

- Cover Letter
- Form FDA 356h

If you have any questions or need further information, please contact me directly.

Thank you.

Respectfully submitted,

Mary L. Zett, Ph.D., CQE
Executive Director, Quality Assurance & Regulatory Compliance
E-mail (secure): mzett@novadel.com
25 Minneakoning Road
Flemington, New Jersey 08822
908-782-3431, ext. 2201
908-782-2445 fax
www.novadel.com

Office of Drug Safety

Memo

To: Norman Stockbridge, MD
Acting Director, Division of Cardio-Renal Drug Products; HFD-110

From: Felicia Duffy, RN, BSN
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

Through: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support
Office of Drug Safety; HFD-420

Date: May 6, 2005

Re: ODS Consult 04-0235-1; Nitro Mist (Nitroglycerin Lingual Aerosol) 0.4 mg; NDA 21-780

This memorandum is in response to an April 26, 2005 request from your Division for a re-review of the proprietary name, Nitro Mist. The proposed proprietary name, Nitro Mist, was found acceptable by DMETS in a review dated October 22, 2004 (ODS Consult #04-0235). Draft labels and labeling were also reviewed at that time. Revised carton and container labels were not submitted for review with this request. However, the package insert labeling was resubmitted for review and comment.

Since the October 22, 2004 review, DMETS identified the proposed proprietary name Nitrolingual PumpSpray and a nebulizer device named Micro Mist as having potential look-alike and/or sound-alike similarities to Nitro Spray.

1. Nitrolingual PumpSpray is indicated for angina pectoris. It is often referred to as "Nitro Spray" in the health care community. Nitro Spray and Nitro Mist look and sound similar because they share the same root name, "Nitro". However, the suffixes (Spray vs. Mist) are orthographically and phonetically distinct. The product characteristics for Nitro Spray and Nitro Mist are identical: strength (0.4 mg/spray), indication for use (angina pectoris), usual dose (1-2 sprays), same active ingredient, frequency of administration (no more than 3 sprays in a 15 minute period), route of administration (lingual), and dosage form (metered spray). Although Nitro Spray and Nitro Mist share overlapping product characteristics, the lack of convincing look-alike and sound-alike similarity of the suffixes minimize the potential for confusion between the two drug products.

2. Micro Mist may sound and look similar to Nitro Mist. Micro Mist is a hand-held, disposable nebulizer attachment (oxygen tubing, mouthpiece, and "T") used for nebulizer treatments. The words "Micro" and "Nitro" may look similar when scripted and can sound similar when pronounced. Both names also

contain the word "Mist". Prescriptions for nebulizer accessories usually come as a generic request and the prescription is filled with whatever brand is available. In the event that the Micro Mist device is prescribed specifically by brand, it will contain a descriptor such as Micro Mist "disposable nebulizer" or "nebulizer attachment"; whereas Nitro Mist will not have an additional descriptor. Furthermore, the majority of prescriptions for nebulizer machines and their accessories are handled through home health care agencies or medical supply companies. Based on the area of distribution, use of descriptors and specialty of use, the potential for name confusion between Micro Mist and Nitro Mist is minimal.

Additionally, DMETS previously reviewed black and white draft labels and labeling for Nitro Mist in ODS consult #04-0235. We requested color labels from the firm through the Division's Project Manager, however, color labels have not be submitted as of yet. DMETS has identified additional comments pertaining to the insert labeling that were not identified in the previous review. In review of the insert labeling for Nitro Mist, DMETS has attempted to focus on safety issues relating to possible medication errors.

A. GENERAL COMMENT

DMETS notes that the sponsor did not submit a patient package insert (PPI). We recommend a PPI be constructed in order to ensure the proper use of Nitro Mist. The PPI should also include the newly added information instructing patients on when to consider reordering Nitro Mist (line 185). We recommend the sponsor follow the currently marketed Nitrolingual PumpSpray as a guideline.

B. DOSAGE AND ADMINISTRATION SECTION

1. In order to ensure proper use of this product, we recommend providing step-by-step instructions with illustrations on how to properly use and administer Nitro Mist.

2. The first sentence of the first paragraph instructs patients that Nitro Mist "[redacted]" This is a vague statement that may lead patients to spray the medication towards the back of the throat, the top of the palate or at the cheek, which may decrease the products efficacy. Since the product is categorized as a lingual aerosol, we recommend specifying that the patient spray Nitro Mist on the tongue.

3. The third and fourth sentences of the first paragraph, "No more than three metered sprays....", and "If chest pain persists...." should be bolded as it contains important information. The current presentation of this information can be easily overlooked.

4. The second and third paragraphs should contain headers labeled "Priming" and "Administering a Dose", 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.

5. 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 Nitro Mist appear prominently at the beginning of the Dosage and Administration section, especially since it must be initially primed with five sprays, and then reprimed with two sprays after being idle for six weeks. Please revise.

In summary, we have no objections to the use of the proprietary name, Nitro Mist. DDMAC finds the proprietary name acceptable from a promotional perspective. Additionally, please submit revised labels and labeling for review. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. DMETS also recommends implementation of the labeling recommendations outlined in this memo that may lead to safer use of the product. If you have any questions or need clarification, please contact the medication errors project manager, Diane Smith at 301-827-1998.

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

/s/

Felicia Duffy
5/26/05 12:21:34 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/26/05 01:51:04 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/26/05 02:15:45 PM
DRUG SAFETY OFFICE REVIEWER

NovaDel Pharma, Inc.
Novel Delivery of Pharmaceuticals

Norman Stockbridge, MD, Ph.D.
CDER - Office of Drug Evaluation I (HFD-110)
Food and Drug Administration (FDA)
Director of the Division of Cardio-Renal Drug Products
Woodmont Office Center Rm 5039
1451 Rockville Pike
Rockville, MD 20872

30th March 2005

cc. Jean W. Frydman

Attention: Cmdr. John David
Central Document Room

Re: NDA 21-780 Nitroglycerin LS, 0.4 mg (Aerosol) –
Subject: **Amendment 17 – Delivery Receipt for Horizon Pharmaceuticals**
Re: Notification Letter for Paragraph IV Certification 505(b)(2)

Dear Dr. Stockbridge:

Enclosed is a copy of the delivery receipt verifying that First Horizon Pharmaceutical Corporation was notified by NovaDel that a Paragraph IV Patent Certification was filed as applicable to NDA 21-780 Nitroglycerin Lingual Spray (LS). This document was inadvertently omitted from the NDA 21-780 Amendment 16 submission (24th March 2005), which contains all other required Paragraph IV Certification documents.

If you have any questions or require further information, please contact the undersigned at 908-782-3431, Ext. 2201.

Respectfully submitted,

Mary L. Zett, Ph.D., CQE
Executive Director, Quality Assurance & Regulatory Compliance

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
NDA 21-780

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NovaDel Pharma Inc.	3/30/05
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
908-782-3431, Ext. 2201	908-782-2445
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
25 Minneakoning Road Flemington, New Jersey 08822	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-780

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Nitroglycerin Lingual Spray, 0.4mg (Aerosol)	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
1,2,3-propanetriol trinitrate ($C_3H_5N_3O_9$)

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Lingual Spray	0.4mg	Lingual

(PROPOSED) INDICATION(S) FOR USE:
Acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☒ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Delivery receipt for First Horizon

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

(active) Facility Registration #

INyX Pharma Ltd., Road 604 San Jose Industrial Zone, Cotto North, Manati PR 00674 (site for commercial finished product manufacturing and testing laboratory)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Delivery receipt for First Horizon

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Mary L. Zett	Dr. Mary Lou Zett, Exec. Dir. QA & Reg. Compliance	3/30/05

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
25 Minneakoning Road, Flemington, New Jersey 08822	(908) 782-3431 ext. 2201

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
Rockville Pike
ville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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.

NOVADEL PHARMA, INC.
NOVEL DELIVERY OF PHARMACEUTICALS

Norman Stockbridge, MD, Ph.D.
CDER - Office of Drug Evaluation I (HFD-110)
Food and Drug Administration (FDA)
Director of the Division of Cardio-Renal Drug Products
Woodmont Office Center Rm 5039
1451 Rockville Pike
Rockville, MD 20872

24th March 2005

cc. Jean W. Frydman

Attention: Cmdr. John David
Central Document Room

Re: NDA 21-780 Nitroglycerin LS, 0.4 mg (Aerosol) –
Subject: **Amendment 16 – Paragraph IV Certification 505(b)(2)**

Dear Dr. Stockbridge:

On 6th July 2004 a letter was addressed to Dr. Throckmorton from Jean W. Frydman, Vice President & General Counsel, on behalf of NovaDel Pharma Inc. In that letter, NovaDel requested the retraction of all Section 13 information from NDA 21-780 submitted on the 16th of June 2005. Subsequent to that time, having further discussion with the Division regarding the Paragraph IV Certification 505(b)(2) requirement, NovaDel now understands that Section 13.0 documentation must be submitted as a pre-requisite for pursuing the 505(b)(2) regulatory strategy.

Also, as discussed with John David, it is understood that by completing Section 13.0 filing requirements NovaDel would effectively satisfy, in full, all specific issues described in FDA Discipline Letter dated 28th February 2005 but does not preclude the FDA's request for further information in those disciplines.

Pursuant to fulfilling the stated requirements enclosed in this submission are the following:

- Form FDA 356h
- Resubmission of FDA Patent Information Form (a copy of the original submitted in the June 2004 filing of NDA 21-780)
- Resubmission of Patent Number 5,869,082, Buccal Non-Polar Spray For Nitroglycerin
- Resubmission of Patent Certification, Paragraph IV Certification (a copy of the original statement submitted in the June 2004 filing of NDA 21-780)
- A copy of the letter sent to G. Pohl Boskamp GmbH & Co. from Dickstein, Shapiro Morin & Oshinksky LLP, dated 21st March 2005, as Notice of Paragraph IV Certification.
- A copy of the FEDEX receipt verifying that the letter sent to Boskamp was received and signed for on 03/23/2005

If you have any questions or require further information, please contact the undersigned at 908-782-3431, Ext. 2201.

Respectfully submitted,

Mary L. Zett

Mary L. Zett, Ph.D., CQE
Executive Director, Quality Assurance & Regulatory Compliance

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-780

INFORMATION REQUEST LETTER

NovaDel Pharma Inc.
Attention: Gary Shangold, M.D
25 Minneakoning Rd.
Flemington, NJ 08822

Dear Dr. Shangold:

Please refer to your new drug application (NDA) dated June 17, 2004, received August 4, 2004 (date removed from Arrears List) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Lingual Spray, 0.4 mg (Aerosol).

We also refer to your submissions dated July 29, August 12, October 26, November 5, November 15, December 6, 2004, January 11 and February 11, 2005.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance Issues: As you reference [redacted] DMF for GTN Basic Solution in support of your NDA please note that there are some outstanding issues that will be directed to their DMF for resolution.

1. Provide complete details of your acceptance testing for the GTN Basic Solution you obtained from [redacted]

Documentation Issues:

1. Update the LOA from [redacted] for [redacted] to include your current company name.
2. Provide letters of authorization (LOA) for DMF's [redacted] and [redacted] Reference all current control aspects for the valve and its components (i.e., full/updated code numbers, volume, page, and date). Explain where the supporting data (e.g., dimensions, specific [redacted] utilized, and qualification testing such as [redacted] and [redacted] studies) are referenced for the [redacted] designated [redacted], the [redacted] and the [redacted] noted in the related drawing.

Drug Product Issues:

1. Confirm the validity of your content uniformity sampling approach (i.e., using [redacted] testing regimes) and conduct comparative testing that includes [redacted] (n = [redacted] as a one-time proof of concept. Provide complete comparative data for all [redacted] sampling stations that includes individual and mean assay and droplet size distribution data that are statistically interpreted across data sets (e.g., %RSDs). Also, change [redacted] to [redacted] your content uniformity criteria in accord with the 'Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products –Chemistry, Manufacturing, and Controls Documentation' guidance document that you cite.
2. Provide GTN priming data to support your claim in the labeling that priming twice after an inactive period of [redacted] weeks is sufficient to assure consistent dosing since more delineating repriming studies (i.e., in the update of 2/11/05) suggest more priming is required to achieve the labeled claim for GTN content even at shorter inactivation times.
3. Explain the basis for the 'interim' designation for your acceptance criteria for the drug product specification (e.g., update of 10/26/04, Amendment #5) and your plans to have final specifications in place.

4. You have provided no batch data to support the use of INyX, P.R. as the commercial manufacturing site. Please submit release data fo[illegible] alidation batches manufactured at this site or site specific stability data.
5. Justify why [illegible] ontent is not included in the drug product specifications.
6. Revise your ovality acceptance criteria to include a specified range as you previously did (e.g.,[illegible]
7. Include acceptance criteria for all the specified degradants in your specifications. Your provision to specify over [illegible] is too vague and not acceptable.
8. Justify the basis for your spray weight specification with attention given to reducing the upper limit value of [illegible] mg/actuation.
9. Concerning the testing for the volume of the valve actuation chamber (i.e., SOP OA 200.9 rev.1. update of 2/11/05. Section 5.4.1, p. 78), please explain the function of the [illegible] What is the relevance of this step to the manufacturing process (i.e., [illegible] before final release testing)?
10. Provide an explanation for how the hole dimensions in the plastic coating of your bottle have been designed to provide an adequate measure of the use of the [illegible] actuations.
11. Provide a diagram of the bottle that clearly depicts the two holes in the coating. Include an explanation of the function of these holes in terms of expected available doses.
12. Provide test procedure [illegible]), its supporting validation work, and where it will be utilized for control function.

If you have any questions, please call:

Mr. John David
Regulatory Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
3/16/05 03:30:29 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-780

DISCIPLINE REVIEW LETTER

NovaDel Pharma Inc.
Attention: Gary Shangold, M.D.
25 Minneakoning Rd.
Flemington, NJ 08822

Dear Dr. Shangold:

Please refer to your dated June 17, 2004, received August 4, 2004 (date removed from Arrears List) new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Lingual Spray, 0.4 mg (Aerosol).

We also refer to your submissions dated July 6, 29, and 30, August 6, December 20, 2004 and January 27, 2005.

We are in the process of reviewing of the Clinical, Clinical Pharmacology and Biopharmaceutics, Pharmacology and Toxicology sections of your submission and have identified the following deficiencies:

CLINICAL

1. There is no replicative (supporting) study to confirm efficacy of this drug.
2. There are no data on tolerance of this drug.
3. The safety database that was submitted is inadequate in the following manner:
    - Too few patients
    - Inadequate duration of follow-up
    - Lack of adequate demographic subgroups (patients > 65 years and African Americans)
4. No QT study was submitted.
5. There is a lack of PK linkage between the drug used in the trial and those compared with in the literature for safety comparisons (adverse events).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTITICS

1. There is no characterization of the metabolic pathway of GTN or determination if the CYP450 or the PgP system is involved in the metabolism of the drug. Information derived from such studies will help determine what drug interaction studies will be required.
2. A mass balance study will be required. Information derived from the mass balance study will help identify possible special populations that will require further assessment (i.e., renal, hepatic, pharmacokinetic gender differences, etc.)
3. There is no assessment of the contribution GTN's metabolites toward efficacy and/or safety.
4. The bioavailability of GTN should be determined.
5. Full pharmacokinetic characterization of GTN will be required, not just the descriptive pharmacokinetics that has been submitted (i.e., volume of distribution and clearance determination).
6. Pharmacokinetics in the targeted population will be required.
7. PK/PD correlation should be explored for GTN and any active metabolites.

PHARMACOLOGY AND TOXICOLOGY

1. A full battery of reproductive toxicity, genotoxicity, and both rat and mouse carcinogenicity studies as described in ICH-55A, ICH-52B, and ICH-51B respectively is required. This may be satisfied by studies done for or by sponsor, or published studies.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. Please note that CMC deficiencies are not included in this letter and will be discussed with you separately. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Mr. John David
Regulatory Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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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

Transmitted to FAX Number:	908-782-2445
Attention:	Mary Lou Zett
Company Name:	NovaDel Pharma Inc.
Phone:	908-782-3431, ext 2201
Subject:	**February 2, 2005 Meeting Minutes NDA 21-780**
Date:	
Pages including this sheet:	

From:	**John David**
Phone:	**301-594-5309**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Meeting between NovaDel and the FDA Division of Cardio-Renal Drug Products

Sponsor:	NovaDel Pharma Inc.
Drug:	Nitroglycerin Lingual Spray
NDA:	21-780
Date of request:	January 26, 2005
Date of confirmation:	January 27, 2005
Date of teleconference:	February 2, 2005
Time:	2:30 – 3:30 pm
Type/Classification:	C/Guidance Meeting
Meeting Chair:	Kim Dettelbach
Meeting recorder:	*John David*

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Kim Dettelbach	Associate Chief Counsel for Drugs, Office of Chief Counsel, GCF-1
Edward Fromm	Chief, Project Management Staff, HFD-110
David Roeder	ADRA, OND/ODE IV, HFD-104
Donald Hare	Special Assistant, Office of Generic Drugs, HFD-600
Denise Hinton	Regulatory Health Project Manager, HFD-110
John David	Regulatory Health Project Manager, HFD-110

NovaDel Attendees:

Jean W. Frydman	Vice President & General Counsel
Arkady Rubin, Ph.D. (via telephone)	Executive Director, Biostatistics and Data Management
Janis Picurro (via telephone)	Director, Regulatory Affairs, Representative from Par Pharmaceutical
Julia Szozda (via telephone)	Senior Associate, Regulatory Affairs R&D, Representative from Par Pharmaceutical
Mary Lou Zett, Ph.D. (via telephone)	Executive Director, Quality Assurance & Regulatory Compliance

Background:
NovaDel Pharma Inc. submitted patent certification in Section 13.0 of their NDA and retracted that section in a letter dated July 6, 2004. NovaDel stated in the letter that they relied solely on its own clinical investigations and published data for their submission.

NovaDel was sent an information request letter, dated January 21, 2005, stating that applications submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, should provide a patent certification against a pharmaceutical equivalent, if any, or if there is no pharmaceutical equivalent, against the closest pharmaceutical alternative. This ensures that listed drugs receive appropriate intellectual property protection and permits FDA to rely on the approval of the closest pharmaceutical alternative in determining the nature and quantity of data required for approval of a new product under section 505(b)(2) of the Federal Food Drug and Cosmetic Act. Because NDA 18-705 is the closest pharmaceutical alternative to NDA 21-780, NDA 21-780 should include patent certification for the patents listed for NDA 18-705, Nitroglycerin Lingual Spray.

The Sponsor's Counsel requested this meeting to discuss this request with a representative from the FDA *Office of the Chief Counsel.*

Introductions:

Discussion with NovaDel:

NovaDel indicated that based on the July 7, 2004 King Pharmaceuticals, Inc. (Civil action # 04-1058) case they did not rely on other investigative studies, instead they relied on their own safety study data and on published literature in the public domain. They believe that their submission is similar to the King case and that they should not be required to submit a patent certification against the closest pharmaceutical equivalent or pharmaceutical alternative product.

The Agency asked what raw and support data were relied on to support this NDA. The Sponsor indicated that publications and journals were used. The Agency explained that the type of information that a 505(b)(2) application may rely on is published literature, the Agency's finding of safety and efficacy for an approved drug so long as an adequate 'bridging study' is performed, and any other data performed by the applicant of the proposed drug product that is needed to support the full report requirements of a *505 (b)(1)* application.

The Agency noted the differences between this application and the King Case. The King Case did not involve labeling changes, Levoxyl drugs were already approved and marketed, the Sponsors submitted additional information to show bioequivalence, there were no changes in conditions, and the Agency did not have to rely on other findings of safety and efficacy. The application was reviewed to assess whether it met the bioequivalence criteria for an AB rating and no additional patent certifications were required. In contrast, NovaDel is seeking initial approval of a drug and they would therefore need information to support the full report requirements of a 505 (b)(1) application.

The Sponsor asked if it would be acceptable to use clinical data and safety/efficacy information from the literature. The Agency indicated that their 505(b)(2) application would have to provide the same full report information as would be required for a 505 (b)(1) application. The Sponsor referenced and quoted page 16 of the King Case. The Agency noted that the approval of the 505 (b)(2) drugs in the case were not an issue since the drugs were already approved and had met the full report approval requirements. The Sponsor noted that they followed the guidance provided from previous meetings with the Division prior to the submission of their NDA and asked if the clinical group would have to make a decision as to whether to continue the review. The Agency stated it would be necessary for the Sponsor to provide adequate data to support their labeling as they can not rely on previous findings of safety and efficacy for nitroglycerin without patent certification.

The Sponsor referenced the November 2003 meeting that indicated the Division informed the Sponsor to produce evidence from clinical trials and published data to support labeling. They also cited page 16 of the King Case and referred to CFR 314.50 and reiterated that they did not rely on other clinical data. The Agency stated that just because data are published does not mean right of reference is given to clinical data and indicated that since the Sponsor is not certifying to a patent this entity would be treated like a New Molecular Entity (NME) as far as efficacy and safety data need to support approval. The Sponsor noted that the material NovaDel referenced may not be sufficient as a full report as there may not be raw data to support certain sections of the labeling, such as the Pharmacology/Toxicology section.

It was explained that the Sponsor still has an opportunity to submit the Patent Certification and Bridging Study, as the regulatory goal date is June 4, 2005, or the reviewers will have to review information that was submitted in the NDA only and rely on nothing else to support safety and efficacy. The Sponsor

noted they did not rely on any other findings and asked if they could be provided information on what raw data is missing. The Agency stated that a Discipline Review Letter will be sent to the Sponsor notifying them of deficiencies noted in the review to date.

The Sponsor noted that there may be one patent at issue. They are prepared to certify but will not submit it if they do not have to. The Agency stated if they seek to rely in any way on a previous finding of safety and effectiveness for another drug, a patent certification will be required. If they choose not to rely on a previous approval in this fashion, they will need to provide full reports (including in most instances raw data) to establish the safety and effectiveness of their proposed drug product.

The Division confirmed that PDUFA Goal Date remains June 4, 2005 and that information submitted to address issues in the Discipline Review Letter in the last 3 months of the review cycle may be considered a major amendment which could extend the review clock 3 months.

The Agency recommended that the Sponsor review the current guidance on relying on data or findings of safety/efficacy and the Citizens Petition of October 14, 2003.

Summary of Main Action Items (Nitroglycerin Lingual Spray)

- The Sponsor may submit the Patent Certification and Bridging Study or submit information to address issues in the Discipline Review Letter.

Meeting recorder: _____
John David
Regulatory Health Project Manager

Meeting concurrence: _____
Kim Dettelbach
Associate Chief Counsel for Drugs

Meeting concurrence: _____
Norman Stockbridge, M.D., Ph.D.

Draft: jd 2/8/05
Final: jd/2/14/05

RD:
Hinton: 2/9/05
Fromm: 2/10/05
Hare: 2/10/05
Roeder: 2/11/05
Stockbridge: 2/11/05
Dettelbach: 2/14/05

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/s/

Norman Stockbridge
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-780

INFORMATION REQUEST LETTER

NovaDel Pharma Inc.
Attention: Gary Shangold, M.D
25 Minneakoning Rd.
Flemington, NJ 08822

Dear Dr. Shangold:

Please refer to your August 4, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Lingual Spray, 0.4 mg (Aerosol).

We also refer to your submission dated July 6, 2004.

We are reviewing the patent certification and clinical sections of your submission and have the following comments and information request. We request a prompt written response in order to continue our evaluation of your NDA.

Applications submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, should provide a patent certification against a pharmaceutical equivalent, if any, or if there is no pharmaceutical equivalent, against the closest pharmaceutical alternative. This ensures that listed drugs receive appropriate intellectual property protection and permits FDA to rely on the approval of the closest pharmaceutical alternative in determining the nature and quantity of data required for approval of a new product-under section 505(b)(2) of the Federal Food Drug and Cosmetic Act. Because NDA 18-705 is the closest pharmaceutical alternative to your NDA 21-780, NDA 21-780 should include patent certification for the patents listed for NDA 18-705, Nitroglycerin Lingual Spray.

If you would like us to reconsider this determination, please contact Mr. John David and ask to schedule a meeting to include a representative of the FDA Office of the Chief Counsel.

If you have any questions, please call:

Mr. John David
Regulatory Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Norman Stockbridge
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Guirag Poochikian , HFD-800

FROM: Stuart Zimmerman

DATE: 1/12/04	IND NO.:	NDA NO.: 21-780	TYPE OF DOCUMENT : Original submission	DATE OF DOCUMENT: June 17/2004, and then 8/4/04(status date- FI)

NAME OF DRUG: Nitroglycerin Lingual Spray, 0.4mg (Aerosol)	PRIORITY CONSIDERATION: High since new NDA	CLASSIFICATION OF DRUG: Chemical Type 3 (New Formulation)	DESIRED COMPLETION DATE: February 4, 2005

NAME OF FIRM: NovaDel Pharma Inc.

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE--NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW

x• OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
• TYPE A OR B NDA REVIEW • END OF PHASE II MEETING • CONTROLLED STUDIES • PROTOCOL REVIEW • OTHER:	• CHEMISTRY REVIEW • PHARMACOLOGY • BIOPHARMACEUTICS • OTHER:

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILTY STUDIES
- PHASE IV STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

• CLINICAL	• PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The applicant refers to their product as "Nitroglycerin Lingual Spray, 0.4mg (Aerosol)" in their 356 h form. This product is for the treatment of [redacted]. From the related IND 64,596 N-002 dated 10/14/04 there is a listing of the foreign marketing history of related products (i.e., see Attachment #1 of scanned images). Attchments #2 and #3 refer to the current labeling (i.e., PI and carton) for the approved NDA 18-705 drug products in HFD-110. There is also reference to the subject NDA holder's proposed immediate container labeling (i.e., Attachment #4). The current DMETS consult results are available as noted in DFS (i.e., ODS Consult #: 04-0235) for this NDA 18-705.

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): Ξ E- MAIL • HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

Attqachment #1:

2.3 FOREIGN MARKETING HISTORY

NovaDel's aerosol nitroglycerin lingual spray is not commercially available in any country nor has it been withdrawn from any market.

Worldwide there are 767 nitroglycerin products currently distributed for the treatment of angina pectoris due to coronary artery disease. Dosage forms include: tablets, capsules, patches, sprays, ointments, and intravenous solutions. (See Appendix A to this Application Summary for a listing of nitroglycerin formulations obtained via Thomson, Micromedex, DRUGDEX ® System).

Of the 767 products available, we were able to identify the following products in sublingual spray dosage form:

ANGIOSPRAY (FM)

- Active-Ingredient
  - GLYCERYL TRINITRATE
- Availability
  - ITALY
- Manufacturer:
  - UCB, Ital.UCB Pharma S.p.A.
    Via Praglia 15
    10044 Pianezza (TO)
    Italy

CORANGIN

- Active-Ingredient
  - NITROGLYCERIN - 0.41 mg/dose
- Availability
  - GERMANY
- Manufacturer:
  - NOVARTIS (GERMANY)Roonstrasse 25, Nurnberg, Germany D-90429
    Business Hours: (49) (911) 2730; (49) (911) 27312653 (Fax)

GEN-NITRO

- Active-Ingredient
  - NITROGLYCERIN - 0.4 mg/actuation
- Availability
  - CANADA
- Manufacturer:
  - GENPHARM (CANADA)37 Advance Road, Etobicoke, ON, Canada M8Z 2S6
    Business Hours: (416) 236-2631; (416) 236-2940 (Fax)

- NDC-Code
  - DRUG IDENTIFICATION NUMBER 02243588

NATISPRAY

- Active-Ingredient
  - GLYCERYL TRINITRATE
- Availability
  - FRANCE
- Manufacturer:
  - Procter & Gamble, Fr.Procter & Gamble Pharmaceuticals France
    96 av Charles-de-Gaulle
    92201 Neuilly-sur-Seine cdx

- Availability
  - ITALY
- Manufacturer:
  - Teofarma, Ital.Teofarma
    Via F.lli Cervi 5
    27100 Valle Salimbene (PV)
    Italy

NATISPRAY (FM)

- Manufacturer:
  - Nativelle, Switz.

NITROLINGUAL

- Form
  - ORAL SPRAY
- Available-Container-Size
  - 13.8-g canister
- Active-Ingredient
  - NITROGLYCERIN - 0.4 mg/spray
- Excipients
  - DICHLORODIFLUOROMETHANE
  - DICHLOROTETRAFLUOROETHANE
  - ETHER
  - FLAVORS
- Availability
  - U.S.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-780

Trade Name:
Generic Name: Nitroglycerin Lingual Spray
Strengths: 0.4 mg

Applicant: NovaDel Pharma Inc.

Date of Application: June 17, 2004
Date of Receipt: August 4, 2004
Date clock started after UN: August 4, 2004
Date of Filing Meeting: August 2, 2004
Filing Date: October 4, 2004
Action Goal Date (optional): June 4, 2005 User Fee Goal Date: June 4, 2005

Indication(s) requested: Acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease.

Type of Original NDA: (b)(1) _____ (b)(2) ____X____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ____X_____ P _____
Resubmission after withdrawal? ____NO___ Resubmission after refuse to file? ___NO____
Chemical Classification: (1,2,3 etc.) ____3_____
Other (orphan, OTC, etc.) ____N/A___

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

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID # _____N/A_____
Clinical data? YES _____ NO, Referenced to NDA # __18-705___

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES

If yes, explain: NDA 18-705 expires February 16, 2010

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

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

NO

Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES

- Was form 356h included with an authorized signature? YES

  If foreign applicant, both the applicant and the U.S. agent must sign. **N/A**

- Submission complete as required under 21 CFR 314.50? YES

  If no, explain: N/A

- If an electronic NDA, does it follow the Guidance? N/A

  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A

- Is it an electronic CTD? NO
- **If an electronic CTD, all certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? YES, _3_years

  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

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

- Financial Disclosure forms included with authorized signature? YES
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

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

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: 64,596

- End-of-Phase 2 Meeting(s)? NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _11/4/03 (clinical)__
  _2/3/04 (CMC)_____

  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES (trade name pending)

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A

- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? NO
  If no, did applicant submit a complete environmental assessment? YES
  If EA submitted, consulted to Florian Zielinski (HFD-357)? NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES

- If a parenteral product, consulted to Microbiology Team (HFD-805)? NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: Nitroglycerin Lingual Spray NDA # 21-780

- Describe the change from the listed drug(s) provided for in this (b)(2) application:
Indication of acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease. Sponsor states inactive ingredients include n-butane as a propellant in place of the propellant used in NDA 18-705 Nitrolingual Spray (nitroglycerin lingual aerosol).

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

NO

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

NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

__X_ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    YES
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # __64,596__

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 2, 2004

BACKGROUND:
NovaDel Pharma Inc. submitted NDA 21-780 Nitroglycerin Lingual Spray as a 505(b)(2) for the indication of acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease. The sponsor states inactive ingredients include n-butane as a propellant in place of the propellant used in NDA 18-705 Nitrolingual Spray (nitroglycerin lingual aerosol).

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Akinwole Williams, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Belay Tesfamariam, Ph. D.	Pharmacologist, HFD-110
Lydia Velazquez, Pharm. D	Clinical Pharmacology, Biopharmaceutist, HFD-860
Stuart Zimmerman, Ph.D.	Chemist, HFD-110
John David	Regulatory Health Project Manager, HFD-110
Denise Hinton	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS:

Discipline	Reviewer	Review Due
Medical:	Akinwole Williams, M.D.	November 15, 2004
Statistical:	Charles Le (James Hung attended)	February 1, 2005
Pharmacology:	Belay Tesfamariam, Ph. D.	October 31, 2004
Chemistry:	Stuart Zimmerman, Ph. D.	February 1, 2005
Biopharmaceutical:	Lydia Velazquez, Pharm. D	February 1, 2005
Regulatory Project Management:	John David	
Other Consults:	N/A	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE ___X___ REFUSE TO FILE _____
*(Dr. Williams noted only 1 female in study, will follow-up with review of women's health initiative)

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

CLINICAL MICROBIOLOGY NA __X____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE ___X___ REFUSE TO FILE _____
*(will assess and report if SAS data sets can be reviewed by 8/13/04)

BIOPHARMACEUTICS FILE ___X___ REFUSE TO FILE _____
- Biopharm. inspection needed: NO

PHARMACOLOGY NA _____ FILE ___X___ REFUSE TO FILE _____
- GLP inspection needed: NO

CHEMISTRY FILE ___X___ REFUSE TO FILE _____
- Establishment(s) ready for inspection? NO
  *(8/5/04 S. Zimmerman scheduled inspection in 3-4 months, NovaDel stated will be ready for inspection by October 2004.)
- Microbiology NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

X_____ Filing issues to be communicated by Day 74.

ACTION ITEMS:

No filing issues conveyed to applicant by Day 74; however, review issues noted by chemistry reviewer will be sent.

Note: 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.

_____
John David
Regulatory Project Manager, HFD-110

RD
Stockbridge 8/31/04
Fromm8-17-04
Karkowsky8-16-04
Williams 8-16-04
Velazquez 8-16-04
Tesfamariam 8-13-04
Hung 8-13-04
Le 8-10-04
Hinton 8-9-04

RD
Stockbridge
Fromm
Karkowsky
Williams
Velazquez
Tesfamariam
Le
Hinton

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/s/

John David
9/1/04 03:49:32 PM

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

Transmitted to FAX Number:	908-782-2445
Attention:	Mary Lou Zett
Company Name:	NovaDel Pharma Inc.
Phone:	908-782-3431, ext 2201
Subject:	**Meeting Minutes** **NDA 21-780**
Date:	August 26, 2004
Pages including this sheet:	4

From:	**John David**
Phone:	**301-594-5368**
Fax:	**301-594-5494**

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Minutes of a teleconference between NovaDel and the FDA Division of Cardio-Renal Drug Products

Sponsor:	NovaDel Pharma Inc.
Drug:	Nitroglycerin Lingual Spray
NDA:	21-780
Date of teleconference:	July 30, 2004
Type/Classification:	C/Guidance Meeting
Classification:	Guidance/to discuss the Nitroglycerin Lingual Spray proposed labeling as related to 505 (b) (2) user fee.
Meeting Chair:	Ed Fromm
Meeting recorders:	John David

FDA Attendees:

Edward Fromm	Acting Chief, Project Management Staff, HFD-110
John David	Regulatory Health Project Manager, HFD-110
Denise Hinton	Regulatory Health Project Manager, HFD-110
Michael Jones	Senior Program Manager, Office of Regulatory Policy, HFD-005

NovaDel Attendees:

Gary Shangold, M.D.	President, CEO
Mary Lou Zett	Executive Director, Quality Assurance & Regulatory Compliance
Rubin Arkady	Statistician

Background:
NovaDel Pharma Inc. submitted proposed labeling on June 5, 2003, that was reviewed by Ms. Tawni Schwemer of the Office of Regulatory Policy. On July 16, 2003 Ms. Schwemer notified NovaDel that based on the submitted proposed labeling the user fee staff did not feel this NDA would be a fee paying 505(b)(2) application. NovaDel was informed that when the NDA is submitted the labeling would be reviewed again and if any changes were made to the proposed labeling, the application may become a fee paying 505 (b)(2) application.

NDA 21-780 was received on June 17, 2004. The electronic labeling was requested from NovaDel and was received via the EDR July 13, 2004. After review of the labeling, Mr. Jones requested additional labeling information from NovaDel on July 26, 2004, to clarify the differences in the two labels. On July 30, 2004, Mr. Jones conducted a comparative review of NovaDel's labeling against their proposed product labeling submitted on June 5, 2003. Mr. Jones notified Mr. Fromm and Mr. David that labeling differences were noted in the 2004 proposed labeling as compared to the June 5, 2003 labeling. There were comparative claims noted that were considered new indications for a use and, therefore NovaDel's application will be considered a fee-paying 505(b)(2) application.

Discussion with NovaDel:
Mr.Fromm referred to a previous telephone conversation with Mr. Jones, in which the 2004 proposed revised labeling for the nitroglycerin lingual spray was discussed. Mr. Fromm informed NovaDel that the proposed labeling was different from the labeling sent in June 5, 2003, and stated that the labeling should have been identical in order to be considered a non fee-paying 505(b)(2) application. The differences noted in the 2004 labeling, as compared to the June 5, 2003 labeling were that comparative claims were included, which are considered new indications for a use and therefore NovaDel's application will be considered a fee-paying 505 (b)(2) application.

NovaDel agreed that some claims were used. Mr. Fromm informed NovaDel of the following comparatives claims in the proposed 2004 package insert. (see attachment 4, section 2.1 of the annotated proposed labeling):

1) Page 3, 3rd block under the **CLINICAL PHARMACOLOGY** section, the entire paragraph.
2) Page 4, 3rd block under the **Pharmacokinetics and Drug Absorption** section, the entire 2nd paragraph.
3) Page 7, 3rd block under the **PRECAUTIONS** section, the entire paragraph.
4) Page 11, 4th block, under the **ADVERSE REACTIONS** section, the entire paragraph.
5) Page 13, 2nd block, under the **DOSAGE AND ADMINISTRATION** section, "3 to".
6) Page 13, 4th block, under the **DOSAGE AND ADMINISTRATION** section, the sentence [redacted]

NovaDel stated that the new label contained language from their study, published literature, and approved labeling from similar drug products. They admitted that some language may indicate a claim but thought these statements, if objectionable, would be stricken from the labeling at the end of the review cycle. It was noted that the labeling was not considered objectionable. Rather the proposed labeling indicates that the application should be considered a fee paying 505(b)(2) application. Mr. Fromm then informed Novadel of the following options:
1) Amend the labeling by removing language as noted above, and pay no fee
2) Retain the labeling as is and pay the user fee.

Mr. Fromm informed NovaDel that an unacceptable for filing letter would be issued because the application is considered a fee paying 505(b)(2) application (because the labeling differed from the June 5, 2003, labeling by including new indications for a use), and a user fee was not paid upon NDA submission. The review date will not start until amended labeling is received or the user fee is paid. Mr. Jones reiterated Novadel's options as stated above and added that they could pay the user fee, and submit a small business waiver and if the waiver is granted the fee would be reimbursed. NovaDel stated they preferred to amend the labeling, remove the noted claims and pay no fee. NovaDel stated that they would email the updated labeling to the Division and Mr. Jones and have the labeling mailed in by August 2, 2004. Mr. Fromm reiterated that an unacceptable for filing letter due to the user fee not being paid would be sent to NovaDel and that a new start date would be issued when acceptable amended labeling is received.

Mr. Jones explained that the FDA should have received a fee initially since the application is considered a fee paying 505(b)(2) application. Mr. Jones also clarified that the unacceptable for filing letter is not a refusal to file letter. The unacceptable letter merely means that FDA expected a fee for the application and a fee was not received. It has nothing to do with whether you application should be filed or not. NovaDel stated that the company would be affected by this issue and asked if the fee was sent in could the letter be avoided. Mr. Jones stated that it could not because the fee should have accompanied the NDA submission or submitted within the 5 day grace period. Mr. Fromm informed NovaDel of the 10 month filing review process. NovaDel voiced understanding of the issuance of the letter and the explanation of the review process.

Summary of Main Action Items (Nitroglycerin Lingual Spray)

- NovaDel will submit a clean copy and red line strikeout version of labeling via email on July 30, 2004 and via mail on August 2, 2004 for review.
- An unacceptable for filing letter will be issued because a fee was not paid upon NDA submission
- An acknowledgement letter will be sent to NovaDel once the labeling is reviewed. If the new labeling removes all comparative claims as noted above, then the application will qualify as a non fee-paying 505 (b) (2) application.

Meeting recorder: _____

John David
Regulatory Health Project Manager

Meeting concurrence: _____

Edward Fromm
Acting Chief, Project Management Staff

Draft: 30Jul04
Final: 25Aug04

RD:
Hinton: 2Aug04
Fromm: 4Aug04
Jones: 12Aug04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
DMETS, HFD-420			LCDR John David	
DATE 8/19/04	IND NO.	NDA NO. 21-780	TYPE OF DOCUMENT DMETS Consult	DATE OF DOCUMENT 8/19/04
NAME OF DRUG Nitroglycerin Lingual Spray LS, 0.4 mg (Aerosol)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Vasodialator	DESIRED COMPLETION DATE 10/19/04

NAME OF FIRM: NovaDel Pharma Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the proposed trade names for NDA 21-780 Nitroglycerin Lingual Spray and provide comments.
The trade names are listed below in order of preference:

1. [redacted]
2. Nitro Mist
3. [redacted]

The application goal date is June 4, 2005.
The proposed labeling is attached and the carton & container labels were filed electronically.

Thank you!

SIGNATURE OF REQUESTER LCDR John David	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/

John David
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Division of Drug Marketing, Advertisement, and Communications

Internal Consult

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

To: LCDR John David, ODE I/DCRDP

From: Catherine A. Miller, Regulatory Review Officer, DDMAC
Iris Masucci, Labeling Reviewer, DDMAC

Date: 8/10/04

Re: **Tradename (nitrogylcerin lingual spray)**
NDA 21-780
Comments on draft PI

In response to your consult request via email on 7/13/04, we have reviewed Novadel Pharma Inc.'s (Novadel) proposed PI for nitrogycerin lingual spray (brand name pending) and offer the following comments from DDMAC.

Clinical Pharmacology

- The Clinical Pharmacology section of the reference listed drug (RLD), Nitrolingual Pumpspray, states "The mechanism by which nitroglycerin relieves anigina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin and presumably, a more favorable supply-demand ratio is achieved." (Emphasis added.) The NovaDel PI does not contain this language. Is the mechanism of action of nitroglycerin now understood?

- The following claims could be used promotionally:

Are the claims supported by substantial evidence?

- The following paragraph (beginning "') appears to be the only clinical study described in the label. Should it be moved to a section titled "Clinical Studies" that would follow the pharmacokinetics information as is typically done?

- Should reference to this be deleted to avoid an implication of benefit for this dose?

- We suggest deletion of the sentence, " In general, statements describing a drug's safety profile belong under the Adverse Reactions section, not with the clinical trial descriptions.

-

Contraindications

- The RLD PI states, "Nitrolingual Pumpspray is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites." However, the NovaDel PI states, " This could be used promotionally to suggest that the NovaDel product is safer because it is not specifically contraindicated for patients who are allergic to or idiosyncratic for other nitrates or nitrites.

- In the paragraph on concomitant use with PDE5 inhibitors, we suggest using only the generic names for the erectile dysfunction drugs.

Warnings

- The warning "The benefits of Trade Name in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use Trade Name in these conditions, careful clinical or hemodynamic monitoring must be used because of the possibility of hypotension and tachycardia" could suggest off-label use. DDMAC recommends that it be deleted unless the use of nitroglycerin lingual spray in patients with acute

myocardial infarction or congestive heart failure is common. If the warning is warranted, DDMAC suggests that stronger wording be used to clearly state that Trade Name is not indicated for those conditions.

Precautions

General

- We suggest deletion of the sentence, "Excessive use may lead to the development of tolerance" because an entire paragraph on tolerance appears below in this section.

- [redacted] The RLD PI states that "...tolerance clearly occurs." The change in wording could be used to suggest that NovaDel's product is safer than the RLD. Do we now know that tolerance rarely occurs?

- [redacted]

Adverse Reactions

- Are any numbers available for the adverse reaction rates with this product? This section describes the ADRs in very broad terms, including the third paragraph describing the placebo-controlled trial. [redacted]

- The claim in the second paragraph of this section, " [redacted] may be used promotionally. Is this claim supported by substantial clinical experience?

Overdosage

- We recommend rewording of the sentence ' [redacted]

  The language here seems somewhat casual for a label.

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/s/

Catherine Miller
8/10/04 02:54:45 PM
DDMAC REVIEWER

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Catherine Miller OMP/DDMAC PKLN RM17B17 HFD-42	LCDR John David

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7/13/04		21-780	DDMAC Consult	7/13/04

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nitroglycerin Lingual Spray	Standard	Vasodilator	9/13/04

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

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☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the labeling for NDA 21-780 Nitroglycerin Lingual Spray and provide comments.
The application was submitted on 6/17/04 as a 505(b)(2) and the labeling, dated 7/13/04 can be located in the EDR.

Thank you!

SIGNATURE OF REQUESTER LCDR John David	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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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/

John David
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-780

Novadel Pharma Inc
Attention: Gary A. Shangold, M.D.
25 Minneakoning Road
Flemington, NJ 08822

Dear Dr. Shangold:

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

Name of Drug Product:	Nitroglycerin 0.4 mg Lingual Spray (Aerosol)
Review Priority Classification:	Standard (S)
Date of Application:	June 17, 2004
Date of Receipt:	June 17, 2004
Our Reference Number:	NDA 21-780

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 16, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 17, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We have reviewed the submission dated June 29, 2004 requesting a waiver for pediatric studies for Nitroglycerin 0.4 mg Lingual Spray (Aerosol). We agree that a full waiver is justified for Nitroglycerin 0.4 mg Lingual Spray (Aerosol) for the indication of acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease for the entire pediatric population. The pediatric population rarely experiences angina pectoris and therefore this product would not likely be used in a substantial number of patients and the absence of adequate labeling would not pose significant risks.

Accordingly, at this time, a full waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any question, please call:

Mr. John David
Regulatory Project Manager
(301) 594-5368

Sincerely,

{See appended electronic signature page}

Edward Fromm
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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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.

/s/

Edward Fromm
7/14/04 02:12:14 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: ODS (Room 15B-08, PKLN Bldg.)			LCDR John David	
DATE 7/13/04	IND NO.	NDA NO. 21-780	TYPE OF DOCUMENT Labeling	DATE OF DOCUMENT 7/13/04
NAME OF DRUG Nitroglycerin Lingual Spray	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Vasodilators	DESIRED COMPLETION DATE 9/13/04

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the labeling for NDA 21-780 Nitroglycerin Lingual Spray and provide comments.
The application was submitted on 6/17/04 as a 505(b)(2) and the labeling, dated 7/13/04 can be located in the EDR.

Thank you!

SIGNATURE OF REQUESTER LCDR John David	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

7 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

John David
7/13/04 11:57:40 AM

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NOVADEL PHARMA INC.
NOVEL DELIVERY OF PHARMACEUTICALS

25 Minneakoning Road, Suite 101
Flemington, New Jersey 08822-1722
Website: www.NovaDel.com

Fax Transmittal

Date:	6th July 2004
To:	**Commander John David**
Company:	Cardio-Renal Drug Products Division, FDA
Fax:	**301-594-5494**
Phone:	301-594-5368
From:	**Mary Lou Zett**
Phone:	**908-782-3431, Ext. 2201**
Fax:	908-782-2445
Pages:	*2 with cover*

COMMENTS: RSVP-ASAP

John, Jean Frydman, NovaDel's General Counsel, who recently joined our organization, had occasion to review Section 13.0 of our NDA 21-780 against 21 USC 355 (b)(2). As a result, we now realize that since NovaDel did not rely on another drug sponsor's application data, Section 13.0 does not apply to NDA 21-780. Therefore, we wish to retract this information from our submission. Consequently, we would also not need to notify other drug sponsor's of our submission, NDA 21-780 Aerosol Nitroglycerin Lingual Spray.

Please see the attached explanation supporting our request to retract all Section 13.0 information previously submitted in NDA 21-780 on 16th June 2004.

John, while we are certain our interpretation of 21 USC 355 (b)(2) is correct, we would appreciate guidance on this matter, as soon as possible, so that we can be sure we are making interpreting the regulation appropriately.

A copy of the attached correspondence has been filed to NDA 21-780.

Thank you for your assistance.

Kind Regards,

Mary Lou Zett

- CONFIDENTIAL -

NOVADEL PHARMA INC.
NOVEL DELIVERY OF PHARMACEUTICALS

VIA COURIER

July 6, 2004

Douglas C. Throckmorton, MD
Director
Division of Cardio-Renal Drug Products
HFD-110
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-780 Nitroglycerin Lingual Spray

I am requesting on behalf of NovaDel Pharma that the Agency retract the Section 13.0 Patent Information section of the submission.

Pursuant to 21 USC 355 (b) (2), an applicant must provide a certification for each patent which claims the drug for which investigations were conducted for approval, but only when the applicant relied upon investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference from the person for which the investigations were conducted.

NovaDel relied solely on its own clinical investigations and published data for this NDA submission. Therefore, the information required for Section 13.0 does not apply and should be retracted from the submission. NovaDel will not provide any notices thereto.

If you have any questions relating to this section only of the submission, please contact me at 908-782-3431 ext.2450.

Sincerely,

Jean W. Frydman
Vice President & General Counsel

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Telephone
(908) 782-3431
Facsimile
(908) 782-2445
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NOVADEL PHARMA INC.
NOVEL DELIVERY OF PHARMACEUTICALS

June 30, 2004

Douglas C. Throckmorton, MD, Director
Division of Cardio-Renal Drug Product
HFD-110, Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Pediatric Waiver Request - NDA 21-780 Nitroglycerin Lingual Spray (Aerosol)

Dear Dr. Throckmorton:

Novadel Pharma Inc. requests a waiver to 21 CFR 314.55 Pediatric Ruling (December 1998) based on the rationale that since the pediatric population rarely experiences angina pectoris the product would not likely be used in a substantial number of patients and, therefore, absence of adequate labeling would not pose significant risks.

NovaDel's position, as stated above, is predicated on expert opinions published by:

1. **The University of Chicago Children's Hospital {As a major tertiary referral center, the Hospital sees children from the Chicago area, the Midwest, and around the world who have the most complex medical problems}**

   "In pediatrics, there are many causes of chest pain. The most common causes for chest pain are musculoskeletal (pain in the muscles or chest wall), pulmonary causes (asthma or pneumonia), and idiopathic causes (no abnormalities found). Chest pain due to cardiac disease is relatively uncommon. 2 cardiac causes of chest pain in children are pain due to inflammation around the heart "pericarditis" and coronary artery type chest pain or angina pectoris. The latter is usually the biggest concern of parents and patients alike though rarely occurs in children and adolescents."

   {http://64.233.161.104/search?q=cache:O8T8TlF1lrwJ:www.ucch.org/sections/cardio/new/chestpain.html+pediatric+angina-pectoris&hl=en&lr=lang_en}

2. **John Hopkins Children's Center for the Cove Point Foundation Patient Education for Congenital Heart Disease.**

   "Each year, six million adult patients in the U.S. consult a doctor because of chest pain. This pain may be caused by a variety of factors, including certain diseases (e.g. pneumonia, pneumothorax, or collapsed lung), physical injuries, asthma, persistent cough, acid reflux syndrome or severe cases of indigestion, as well as by defects or

diseases pertaining to the heart and/or the blood vessels. Among the more dangerous causes of chest pain are heart diseases. These may affect the heart muscle itself or the vessels, known as the coronary arteries, which supply it with oxygen-rich blood. If the coronary arteries are unable to do their job properly because of blockages or other causes, the patient may experience chest pain known as angina pectoris. In severe cases, where the blood supply to the heart muscle is significantly disrupted, a heart attack may occur.

Unlike adults, children rarely have chest pain that is related to cardiovascular disease. "

{http://www.pted.org/htms/chest1.htm}

3. **An excerpt from Harrison's 15th edition of Principles of Internal Medicine (Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. McGraw-Hill [New York]; 2001: page 1401...describes the primary angina pectoris population as:**

   "Males constitute approximately 70% of all patients with angina pectoris and an even greater fraction of those younger than 50 years of age. The typical patient with angina is a 50- to 60-year-old man or 65- to 75-year-old woman who seeks medical help for chest discomfort..."

If you require more information or have any questions, please contact me directly.

We look forward to a favorable response.

Respectfully submitted,

Mary L. Zett, Ph.D., CQE
Executive Director, QA & Regulatory Compliance
NovaDel Pharma Inc.
Phone 908-782-3431, Ext. 2201
Fax 908-782-2445

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Cc: J. David, FDA
E. Fromm, FDA
G. Shangold, NovaDel

JONES DAY

222 EAST 41ST STREET • NEW YORK, NEW YORK 10017
TELEPHONE: (212) 326-3939 • FACSIMILE: (212) 755-7306

Direct Number: (212) 326-6502
jgmarkey@jonesday.com

009102-999032 June 16, 2004

VIA FACSIMILE AND REGISTERED MAIL
RETURN RECEIPT REQUESTED

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

Dear Sir or Madam:

We represent NovaDel Pharma Inc. ("NovaDel" or "Applicant") 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/S-12 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)(B) of the Federal Food, Drug and Cosmetic Act ("the 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 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 ("NovaDel's Products") before the expiration of the '925 patent.

2. The NDA for the NovaDel Products, nitroglycerin lingual sprays, 400 mcg per spray was accepted for filing by the FDA on ____, 2004 and was assigned the number 21-780

3. The active ingredient of the proposed drug products is nitroglycerin; the strengths are 400mg and the dosage form for each strength 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 by Applicant.

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

DETAILED FACTUAL AND LEGAL BASIS FOR NON-INFRINGEMENT OF U.S. PATENT NO. 5,186,925 UNDER § 505(b)(3)(B) (FDC Act), AND 21 U.S.C. § 355(b)(3)(B)

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.

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_8 to C_{12} fatty acid triglyceride. Claim 5 depends from claim 4 and limits the saturated natural oil to rape oil.

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

To establish infringement every limitation set forth in a claim must be found in accused product, either literally or under the doctrine of equivalents. *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir.), *cert. denied*, 116 S. Ct. 515 (1995). The first step in an infringement analysis is determining the meaning and scope of the patent claims. *Markman v. Westview Instrument, Inc.*, 52 F.3d 967 (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 976. 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.* 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. *Dolly, Inc. v. Spalding & Evenflow Cos.*, 16 F.3d 394 (Fed. Cir. 1994).

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 insubstantial differences between the elements of the claimed invention and the accused product. *Warner-Jenksinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997); *Upjohn Co. v. Mova Pharmaceutical 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."). The burden is on the patent owner to establish infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

NovaDel's Products do not infringe any claim of the '925 patent, literally or under the doctrine of equivalents, for at least two reasons. First, claims 1-5 of the '925 patent are limited to nitroglycerin pump sprays that contain ethyl alcohol. In contrast, NovaDel's Products do not contain any amount of ethyl alcohol. Because NovaDel's Products lack ethyl alcohol, a requirement of the claims, there can be no literal infringement as a matter of law. *Dolly, Inc. v. Spalding & Evenflow Cos.*, 16 F.3d 394 (Fed. Cir. 1994).

Second, claims 1-5 of the '925 patent, as properly construed, are limited to "pump sprays," which, as used in the claims of the '925 patent, are limited to sprays that do not contain propellants. Although the phrase "pump spray" is set forth in the preamble of the claim, in cases where, as here, the claim drafter purported to use both the preamble and the body 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 1241, 620-21 (Fed. Cir. 1995). During the prosecution of the application that ultimately issued as the '925 patent, the applicant repeatedly characterized the alleged invention as a "pump spray," and distinguished

the claims over the cited art, which used propellant sprays, by asserting that the claimed "pump spray" does not contain propellants. Accordingly, claims 1-5 of the '925 patent are limited to "pump sprays," or sprays that do not contain propellants. NovaDel's Products do not use "pump sprays," *i.e.*, sprays without propellants. Rather, the NovaDel Products use gas-pressurized propellants, 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.

In addition, NovaDel's Products do not contain an equivalent to either of the above missing claim limitations. In particular, NovaDel's Products completely lack ethyl alcohol, and fail to contain any element that could be considered an equivalent to ethyl alcohol. Likewise, NovaDel's Products do not contain the equivalent of a "pump spray." 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., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir.), *cert. denied*, 116 S. Ct. 515 (1995). 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 "pump sprays," rather than gas-pressurized propellant systems. It is well settled that "clear assertions made during prosecution in support of patentability" will create an estoppel. *Id.* at 1579. In view of the assertions the applicant made during prosecution, the patentee is estopped from asserting a range of equivalents that would encompass gas-pressurized propellant-containing formulations, such as the NovaDel Products. Accordingly, NovaDel's Products do not infringe any claim of the '925 patent under the doctrine of equivalents.

III. CONCLUSION

For the foregoing reasons, no claim of the '925 patent will be infringed, either literally or under the doctrine of equivalents, by the manufacture, use, sale or offer of sale of NovaDel's 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.

Very truly yours,

James G. Markey
Counsel for NovaDel Pharma Inc.

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NovaDel Pharma Inc.
Novel Delivery of Pharmaceuticals

June 16, 2004

Douglas C. Throckmorton, MD
Director
Division of Cardio-Renal Drug Products
HFD-110
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-780 Nitroglycerin Lingual Spray

Dear Dr. Throckmorton:

Pursuant to 21 U. S. C. 355(b)(2) under Section 505(b)(2) of the Food, Drug and Cosmetic Act regulated by 21 CFR 314.54, NovaDel herewith submits NDA 21-780 for an Aerosol Nitroglycerin Lingual Spray for approval.

In compliance with 21 CFR 314.50(i) and 21 CFR 314.52 full patent certification is duly provided. We respectfully request 3 year patent exclusivity of Waxman-Hatch under 21 CFR 314.50(j); 314.108(b)(4) and (5) predicated on the fulfillment of our requirement to conduct clinical investigations, other than Bioavailability (BA) and/or Bioequivalence (BE). {FR Vol. 59, No. 190, October 3, 1994, pg. 50338.}

We bring to your attention the fact that this submission is a request for approval of the 15mL —dose size) aerosol bottle of NovaDel's Aerosol Nitroglycerin Lingual Spray. This submission contains a full report of up to six months for—stability lots of the 15mL bottle. Up to this point, we understand that the Agency did advise us that we would be permitted to submit our approval request for both the 15mL —— bottle sizes, with the submission of —15mL and —— stability lots.

A User Fee Statement is provided in lieu of User Fee Form FDA 3397. Confirmation of NovaDel's qualification for "Exclusion" status was received by NovaDel on 16th July 2003 from Ms. Tawni Schemer, CDER's User Fee Staff representative. , and is attached to that User Fee Statement.

25 Minneakoning Road
Flemington
New Jersey 08822
Telephone (908) 782-3431

Facsimile (908) 782-2445
www.novadel.com

Relevant to NovaDel's User Fee Exclusion status, labeling discussions took place between NovaDel and the Cardio-Renal Drug Products Division and specific guidance was communicated to NovaDel regarding the Agency's requirements that, in constructing our 505(b)(2) application, we should specifically refrain from referring to proprietary data in any other sponsor's NDA and from merely copying the existing labeling of any other approved nitroglycerin product without independently supporting any statements in such labeling. Rather, we were instructed specifically to be certain to justify any statements that we might make in our proposed labeling with either our own data or information accessed from published literature.

Accordingly, wherever appropriate, NovaDel's product labeling is supported by data from clinical studies conducted by NovaDel Pharma Inc. and/or published findings from other sources, in accordance with conditions established during NovaDel's pre-NDA Meeting with FDA held on November 4, 2003.

We believe that the Agency will nonetheless be reassured that our proposed (current) labeling remains consistent with approved labeling for a similar nitroglycerin lingual spray product, Nitrolingual® Pumpspray (First Horizon Pharmaceutical Corporation) and the recently approved labeling for the sublingual nitroglycerin tablet Nitrostat® (Southward Pharmaceuticals, Inc., previously Parke-Davis' product). Important statements in NovaDel's proposed labeling approach the level typical for class labeling and reflect the current understanding of the mechanism of action and benefits and risks associated with nitroglycerin therapy for the acute relief and acute prophylaxis of anginal attacks.

Submission Administration:

The number of required copies to be submitted was confirmed with Cardio-Renal Drug Products Division Project Manager, Mr. Edward Fromm, as follows:

Full set of 15 volume –

- One Archival Copy
- Four Review Copies

Volume 1, only

- Desk Copy to Edward Fromm

In accordance with 21 CFR 314.50(d)(1), a Field copy will be sent to the following two offices:

- New Jersey District (NWJ-DO)
- Waterview Corporate Center
- 10 Wateview Blvd., 3rd Floor
- Parsippany, NJ 07054

- Philadelphia District (PHI-DO)
- 900 U.S. Customhouse
- 2nd & Chestnut Sts.
- Philadelphia, PA 19106

In preparation and compliance with 21 CFR 314.50(e) sample submission requirements, the NDA 21-780 Review Copy containing Section 4.0 of the CMC submission requirements, as per *CDER Guideline for Submitting Samples and Analytical Data for Methods Validation, III, B,* is labeled as "Review Copy #1".

-

For questions concerning this submission, please contact:

Mary L. Zett, Ph.D., CQE
Executive Director
QA & Regulatory Compliance
NovaDel Pharma Inc.
25 Minneakoning Road
Flemington, New Jersey 08822
Phone 908-782-3431, Ext. 2201
Fax 908-782-2445

Or,

Gary A. Shangold, MD
President & CEO
NovaDel Pharma Inc.
25 Minneakoning Road
Flemington, New Jersey 08822
Phone 908-782-3431, Ext. 2150
Fax 908-782-2445

Respectfully Submitted,

Gary A. Shangold, MD
President & CEO

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Minutes of a Pre-NDA (CMC) Meeting between NovaDel Pharma and the FDA

Date: February 3, 2004

Application: IND 64,596
Nitroglycerin Aerosol Spray for Acute Angina

Applicant: NovaDel Pharma, Inc.

Subject: Pre-NDA (CMC) Meeting

FDA participants

Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Edward Fromm, HFD-110, Regulatory Health Project Manager

NovaDel Pharma

Gary Shangold, M.D., President and CEO
Harry Dugger III, Ph.D., Chief Science Officer
Tom Murray, Director, Manufacturing and Production
Mohammed Ab Del Shafy, Vice President, Pharmaceutical Development
Dongemei Wang, Director, Analytical Research

Background

A pre-IND meeting was held on September 28, 1999 for this drug and CMC related issues were discussed as well as the clinical and pharmacokinetic studies needed prior to submission as a 505(b)(2) NDA. An IND for the drug was submitted on April 22, 2002. The sponsor believes that their aerosol spray system using a butane propellant will provide for more reliable stability and potency of the product over time.

NovaDel met with the Division on November 4, 2003 to discuss the data they had accumulated so far and their planned NDA submission in the first quarter of 2004. During this meeting, the Division notified the sponsor that 6 months of primary accelerated and room temperature stability data would be needed at the filing of the NDA. NovaDel believes that it will have these data by May 2004 and requested today's meeting to discuss other CMC issues with the Division prior to a planned NDA submission in June 2004.

Meeting

Dr. Srinivasachar opened the meeting by noting that we have reviewed the sponsor's background document and have the following comments and recommendations:

Drug Substance

- Dr. Srinivasachar asked if the [redacted] used for production was the same grade as that used in the clinical trials. The sponsor replied that the same grade of [redacted] used in the clinical trials will be used in production batches of the drug product. They noted that they have changed the bottle used to hold the spray but have not changed the spray valve assembly in any way from that used in the clinical trials. This change in bottle configuration has led to a very low leakage rate. Dr. Srinivasachar asked [redacted] NovaDel replied that they do have a COA (Certificate of Analysis) for it and that it was listed in the USP Compendium, but under another chemical name. They added that the [redacted] that they are using [redacted] Dr. Srinivasachar said that

the sponsor should put all applicable information and testing regarding [redacted] in the appropriate section of their NDA.

- Dr. Srinivasachar asked if an identification test had been specified for the drug substance. NovaDel replied that batches of drug substance would be compared by IR spectrum and other standard testing.

Drug Product

- Dr. Srinivasachar asked what product size of the aerosol spray they were planning on marketing. The sponsor said they were planning on using a [redacted] 15 ml bottle of the nitroglycerin spray for marketing. [redacted] the 15 ml bottle would likely contain [redacted] although they are leaning toward [redacted] dose configuration [redacted]
- Dr. Srinivasachar noted that the sponsor has performed the test for Content Uniformity under the USP weight variation criteria for oral solutions rather than the Guidance for Metered Dose Inhalers. Without persuasive evidence, this test would be considered insufficient for demonstrating Content Uniformity. The sponsor replied that they used the weight variation method to directly correlate the amount of nitroglycerin delivered and the weight of lingual spray. [redacted] They believe that because the nitroglycerin mixture is a homogenous solution, the weight variation method is more accurate for demonstrating content uniformity.

  Dr. Zimmerman noted that there was [redacted]

- An identification test is needed for the drug product. NovaDel said that they are using [redacted] right now to [redacted] and asked if this was acceptable. Dr. Srinivasachar replied that the [redacted] would provide acceptable specificity.
- Actual values for degradation products are needed, not just less than a certain percent as currently listed in the background document. The sponsor noted that there are no USP standards for the degradants (e.g., [redacted], but they are diligently trying to secure purified reference standards for these materials to enable better analytical capability.
- It is important that analytical results be reported as a percentage of label claim to facilitate assessment.
- [redacted] method-what is the sampling plan for this test? NovaDel explained that the [redacted] The actuation mechanism for the equipment used to measure [redacted] is very reliable compared to the human firing technique and may be expected to help assure overall performance in a manner that offers stability assessment as well. Dr. Srinivasachar said the test was acceptable provided it had been fully validated. The test results should also be cross validated with the clinical trial bottles and valves.
- Documentation should be provided to show that enough butane is inserted into the spray bottle to ensure positive pressure and that the leakage rate is minimal and conforms to standards. The sponsor said they would supply these data and noted that leakage data would be submitted at every stability stage and when batches are made post-approval. Dr. Srinivasachar reminded the sponsor that USP tests for propellants should also be done (e.g., water content, boiling pt, estimate of residue on boiling).
- Extraction studies-how was this demonstrated? Has the spray valve been used with other approved products? NovaDel replied that a variety of solvents, including [redacted], were used for the [redacted] studies and they were found to be satisfactory for the bottle and spray assembly. They noted that the current spray valve has not been used in other marketed products. Dr. Zimmerman reminded the sponsor that a DMF

would be needed for the [redacted] and its components and that if the supplier of the [redacted] should change, equivalency with the prior [redacted] system would need to be demonstrated. There was also the need to have any secondary DMFs identified that relate to the various component parts of the [redacted] system.

- Stability studies-there is no 9 month room temperature station specified in the protocol; this timepoint plus accelerated stability data at 0, 1, 3, and 6 months are needed when submitting the NDA. Reduced testing is not appropriate until after approval of the product. NovaDel said they will have [redacted] production batches, one of the 15 ml size bottle and [redacted] Dr. Srinivasachar asked if the sponsor has experienced any stability failures in the data collected to date. The sponsor said they have not had any problems so far, although they are carefully looking at the accelerated stability data (40°C/75 RH) as there is some indication that the valve assembly could be affected at temperatures above 60°C. Dr. Srinivasachar suggested that intermediate stability data (30°C/60% RH) should be collected for 12 months, as this could support approval if the valve should fail (e.g. leak testing failure) when exposed to the accelerated temperature and humidity conditions. NovaDel agreed to include the intermediate testing change in their stability protocols. Dr. Srinivasachar asked that a revised stability protocol be submitted to the Division as soon as possible.
- Specifications need to be finalized and not just listed as "interim specifications".
- The leakage rate result values need to be expressed in terms of both average and individual values and included in the acceptance criteria.
- Total fill weight needs to be specified as a range and not open-ended as "[redacted].
- Priming/Repriming Study-NovaDel said that a study to test the longevity of the initial priming of Nitroglycerin Aerosol Spray was underway and would run for 8 weeks. It appears that 2 [redacted] sprays are needed to achieve full delivery (prime) of the system, but that the exact number has yet to be determined pending results of the study. The sponsor noted that their tests so far have shown that there is no loss of the nitroglycerin mixture due to evaporation when a spray is actuated.
- The temperature cycling study proposed by the sponsor is acceptable. The additional control provision of monitoring the [redacted] was discussed and considered to be a positive assessment on valve performance.
- The sponsor will need to justify the microbial test for the nitroglycerin spray (microbial limits or bio-burden). Dr. Srinivasachar suggested that whatever test is chosen, it should be done when the spray product is initially manufactured and at the expiration date. Testing should also be done at the 6 month room temperature and accelerated timepoints. NovaDel noted that because there is no water or air in the drug product, they believe that there is very little chance of microbial growth in the drug product. Nevertheless they will conduct one of the tests listed above and will list this one-time test under drug product specifications [redacted] in the NDA submission. They added that no sterility tests have been planned or completed on this drug product as these tests are not needed because the product is being sprayed into an oral cavity.
- The explosive safety tests conducted by the sponsor appear to be acceptable.

Facility Inspections

- Dr. Srinivasachar asked how many facilities would be eligible for inspection. NovaDel replied that the facilities are 1) Flemington, NJ-quality control site, 2) [redacted] 3) [redacted] (contracted out facility). Dr. Zimmerman asked that the CFN# be included for each of these sites when the NDA is submitted to facilitate inspection of facilities.

Summary of Main Action Items

- Dr. Srinivasachar asked that the sponsor send in a revised specification table and stability protocol for the drug product.
- The Division will assess the issue of Content Uniformity and related sampling issues (i.e., intervals selected and extent of GTN assay testing) internally and will provide feedback to the sponsor.

Minutes Preparation: _____
Edward Fromm

Concurrence, Chair: _____
Kasturi Srinivasachar, Ph.D.

Drafted/ef: 2/8/04-2/19/04

Rd: SZimmerman-2/12/04
KSrinivasachar-2/18/04

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

/s/

Kasturi Srinivasachar
2/23/04 08:52:55 AM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(908) 782-2445
Attention:	Dr. Gary Shangold
Company Name:	NovaDel Pharma Inc.
Phone:	(908) 782-3431
Subject:	**Minutes of a Meeting w/FDA, November 4, 2003** **IND 64,596** **Nitroglycerin Aerosol Spray**
Date:	
Pages including this sheet:	
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Appears This Way
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Minutes of a Pre-NDA Meeting between NovaDel Pharma and the FDA

Date: November 4, 2003

Application: IND 64,596
Nitroglycerin Aerosol Spray for Acute Angina

Applicant: NovaDel Pharma, Inc.

Subject: Pre-NDA Meeting

FDA participants

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Thomas Marciniak, M.D., HFD-110, Medical Team Leader
Akinwole Williams, M.D., HFD-110, Medical Officer
Elena Mishina, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Edward Fromm, HFD-110, Regulatory Health Project Manager

NovaDel Pharma

Gary Shangold, M.D., President and CEO
Harry Dugger III, Ph.D., Chief Science Officer
Arkady Rubin, Ph.D., Executive Director, Biostatistics and Data Management
Tom Murray, Director, Manufacturing and Production
Paul S. Decker, Manager, Clinical and Regulatory Affairs

Background

A pre-IND meeting was held on September 28, 1999 for this drug and CMC related issues were discussed as well as the clinical and pharmacokinetic studies needed prior to submission as a 505(b)(2) NDA. An IND for the drug was submitted on April 22, 2002. The sponsor believes that their aerosol spray system using a butane propellant will provide for more reliable stability and potency of the product over time. NovaDel intends to submit a 505(b)(2) application in the fourth quarter of 2003.

Meeting

Dr. Throckmorton noted that the Division had an opportunity to review the sponsor's questions in their background package and have the following comments:

Question #1

NovaDel proposes to file our NDA under 505(b)(2), with cross-reference to NDA 18-705. Is this acceptable?

Dr. Throckmorton asked if the sponsor had right of reference to the data in NDA 18-705 (Pohl-Boskamp, Nitrolingual Pumpspray). NovaDel replied that they did not, but would like to rely on the Agency's findings of safety and efficacy for this NDA. Dr. Throckmorton noted that because of various legal challenges to the provisions of the 505(b)(2) act, the Division cannot use data from the NDA 18-705 application without right of reference from Pohl-Boskamp, the NDA holder. Furthermore, this precludes our using sources such as the PDR

(Physician's Desk Reference) and SBA (Summary Basis of Approval) to support the application. The sponsor will need to use its own data, data from studies not published, or published literature to justify the labeling for the product. Dr. Throckmorton noted that even pre-clinical sections of the labeling (e.g., carcinogenicity, genotoxicity) would need to be supported by the sponsor's submission. The sponsor asked if they should send in the actual articles or just references to the articles. Dr. Throckmorton replied that they should submit the actual articles and rationale for approval based on these references and any other data they wish to include.

NovaDel said that they believe that the 505(b)(2) regulations allow them to rely on the NDA 18-705 application and asked about the path to challenge the Division's position on this issue. Dr. Throckmorton said the sponsor should submit its arguments (legal and otherwise) to the Division, and he would find out the best Office to comment on their questions. NovaDel noted that there seems to be class labeling for the nitroglycerin products and asked if this information was pertinent to a successful challenge to rely on the safety and efficacy of the NDA 18-705 application. Dr. Throckmorton replied that it was important and should be included in their submission.

Dr. Throckmorton noted, for clarification, that the sponsor has two avenues available to getting their nitroglycerin spray NDA filed:

1. Submitting their data and then convincing the Agency that they should be allowed to rely on the FDA's findings of safety and efficacy for NDA 18-705.
2. Submitting their data, plus published literature to justify the labeling intended for the product. Dr. Throckmorton said that the fact the sponsor conducted a clinical and pharmacokinetic study for this product would increase the chances that the application would be filed, although approvability, of course, would have to be determined later. He encouraged the sponsor, prior to submitting the NDA, to send in a summary of the data sources they intend to use to support their application.

Question #2

NovaDel proposes to number each volume of the NDA independently. Is this acceptable?

Dr. Thockmorton said the sponsor should number each volume consecutively.

Question #3

Because this is a 505(b)(2) submission, as determined by the Agency, NovaDel proposes to cross reference the Nitrolingual Pumpspray NDA (NDA 18-705) for all nonclinical pharmacology and toxicology data. Should NovaDel include a copy of the Summary Basis of Approval (SBA) in this section for ease of review?

Please see discussion above. Dr. Throckmorton said that if the Agency rules that NovaDel may rely on the FDA findings of safety and effectiveness for NDA 18-705, then the sponsor should include the SBA in its NDA submission.

Question #4

As a trade name has not been developed, is it acceptable to file with "TRADE NAME" rather than actual trade name for the NDA?

Dr. Throckmorton said it was acceptable and that Mr. Fromm could be contacted for further information about the trade name review process here at the Agency.

CMC Questions

Question #5

The propellant for the oral aerosol nitroglycerin spray is n-butane. Tests to determine the explosive potential of the nitroglycerin solution (Basic Solution) and the flammability of the spray delivered were requested by

FDA. These studies were carried out and demonstrate that there is no explosive potential for the basic solution and the spray has no effect on glowing wood or metal or on an open flame unless sprayed into the flame from a distance of 6 inches or less. Even in the latter case, the changes in the flame structure returned to normal within seconds with no lasting effects. In which section of the NDA should NovaDel place these reports?

NovaDel noted that the ——solution was not explosive and asked what section of the NDA should this information be placed. Dr. Srinivasachar recommended that this data be placed in the section that describes the physical properties of the ——solution.

The sponsor noted that they had conducted one-time tests for priming and re-priming of the spray, as well as for sterility of the solution, and asked in what section should they place these data. Dr. Srinivasachar replied that they should put these data in the Specifications section, unless they are related to the stability of the solution.

Dr. Zimmerman asked if testing was done for moisture for the product. The sponsor responded that the —— solution was not tested for moisture, but that n-butane was tested for moisture.

Questions #6 & #7

To date, long-term stability data (18 months of a planne(——are available for — batch containing —bottles which is about —of the expected manufacturing batch size (——bottles) of drug product. This clinical batch differs from the commercial product in that type — lass was used (commercial product will use type lass) and the ——is different but still contains a ——material as did the one used on the type lass bottle. Will this be sufficient to start review with accelerated stability data to be supplied as available?

NovaDel would file stability data on this clinical batch and supplement it with stability data from — process validation batches (— batches using the 15 mL bottle to deliver — doses and ——at —of the anticipated manufacturing batches ——. Should this data be submitted as available or with the 4 month update? After approval of the NDA, NovaDel would manufacture full-scale commercial batches for FDA review.

Dr. Srinivasachar noted that the data submitted to date was just supportive stability data and not the primary stability data needed for approval. He said that at least 6 months of room temperature and accelerated stability data would be needed at the time of filing of the NDA and that such studies should include leakage rate data. Six additional months of stability data (room temperature) would then have to be submitted during the review period to ensure a viable expiration date.

Dr. Zimmerman noted that the sponsor should provide content uniformity data for the spray as is required by the draft provisions in "Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products." In other words, they should demonstrate that the first actuation of the spray is equal in content to the last spray from the bottle throughout the entire expiry dating period. NovaDel replied that they believe that they are not bound by this requirement as they thought it was for only metered dose inhalers. Dr. Srinivasachar mentioned that these basic guidance control principles are relevant for this stage of drug development – apart from what may have been relevant at initial IND submission stage. Dr. Zimmerman indicated that content uniformity data were also required by the USP for this type of delivery system and that there was a downward trend for the content of the nitroglycerin at the 18-month stability time point even through the weight of the spray jet was constant; this deserved greater monitoring attention. He also indicated a need to examine the priming characteristics of the delivery system (e.g., doses needed to prime and holding times for primed system). The sponsor would be expected to provide more supporting experimental information to justify their position not to conduct content uniformity testing. Novadel noted that the spray solution is homogenous and they believe that they could demonstrate uniformity by testing the weight of spray delivered per actuation.

Question #8

Because they are not intended for commercialization, NovaDel proposes to include only the stability data for the two strengths of drug product that were used only in the clinical trials, namely the 0.2 mg and 0.8 mg per actuation formulations in the type [redacted] glass bottles using the same valves. Does information for the 0.2 mg and 0.8 mg clinical batches need to be filed with the NDA or is it sufficient to cross-reference the IND?

NovaDel noted they have 3 months of room temperature and accelerated data stability data for these strengths. Dr. Srinivasachar said that they could put these data in the NDA, but it is not absolutely necessary.

NovaDel noted that in the clinical trials, the 0.8 mg dose was obtained by spraying 0.4 mg twice in repetitive fashion and asked if this was acceptable. Dr. Throckmorton said it seemed acceptable, but asked the sponsor to document how the testing was done and under what conditions. Dr. Zimmerman indicated that attention should be given to the timing between doses that are given in a sequence in view of the expected cooling effect.

Clinical Questions

Question #9

There is very little safety data to be addressed for the two clinical studies conducted by NovaDel. Only 7 subjects had adverse events in the Phase II/III study; no deaths or other serious adverse events occurred, and no subject discontinued due to an adverse event. Laboratory data were collected only at Screening. For the reasons noted above, is it acceptable to cross-reference the pharmacokinetic study and dose-ranging study reports in lieu of a conventional ISS (NDA Section 8H)?

Dr. Throckmorton said it was acceptable but noted that sponsor would need to justify all aspects of the labeling for the product. For example, the route of administration, interdosing interval, and repetitive dosing instructions in the labeling will need to be justified.

Dr. Throckmorton noted that the primary endpoint for the clinical trial appeared to be time to moderate angina, and not time to maximal exercise as is usually the case in angina trials. Time to moderate angina would be acceptable as an endpoint if linked to symptom-limiting maximal exercise, so in a sense, time to moderate angina would then be a surrogate for time to maximal exercise limited by symptoms. The sponsor replied that for their study, time to moderate angina and time to maximal exercise were in fact the same thing, and they would clarify this point in their NDA submission.

Dr. Throckmorton suggested that for the safety and efficacy sections of the NDA, that the sponsor lead the efficacy section with data from their own trials followed by literature supporting the efficacy of the nitroglycerin spray. For the safety section of the NDA, the sponsor may want to lead with literature references describing the extensive safety experience with nitroglycerin followed by their own safety data.

Question #10

Is it acceptable to limit the ISE to the reference to the dose-ranging study 99-003 with emphasis on the justification of 0.4 mg nitroglycerin lingual spray as the most appropriate commercial dose?

Dr. Throckmorton said it was up to the sponsor to determine what dose was suitable for marketing, but noted that, if adverse events were present at a higher dose, these would need to be described in the labeling. He also noted that data on the lower and higher doses of the drug were important in demonstrating the efficacy of the drug.

Dr. Mishina noted that delivery of the 0.4 mg dosage strength was less than stated (i.e., <0.4 mg were actually being delivered per actuation) and asked the sponsor to provide clarification on this phenomenon in their NDA submission. Additionally, the exposure to nitroglycerin (both Cmax and AUC values) after the 1.2 mg dose with the Aerosol Spray was less than historic data for 0.8 mg dose with the Pumpspray. The sponsor should evaluate the

possible tolerance development if the next dose were to be administered within 15 minutes, since they do not have data on multiple dosing with the proposed spray formulation.

Question #11

Is modification and enhancement of the original efficacy analysis, as outlined in Section 11.2.2 and Appendix C, acceptable?

Dr. Throckmorton said it was acceptable.

Summary of Main Action Items

- Dr. Throckmorton stated that he did not believe the sponsor would be able to rely on the FDA's finding of safety and efficacy for NDA 18-705 and instead would have to use its own data, data from studies not published, or published literature to justify the labeling for the product. He noted, however, that the sponsor could challenge the Division's position by submitting arguments as to why their product should not be allowed to rely on FDA's finding of safety and efficacy for NDA 18-705.
- Dr. Srinivasachar stated that at least 6 months of room temperature and accelerated primary stability data would be needed at the time of filing of the NDA. Six additional months of stability data (room temperature) would then need to be submitted during the review cycle to justify a viable expiration date. The sponsor was encouraged to request a separate CMC meeting to discuss appropriate testing and controls for this delivery system.

Minutes Preparation: _____
Edward Fromm

Concurrence, Chair: _____
Douglas C. Throckmorton, M.D.

Drafted/ef: 11/7/03-11/18/03

Rd: SZimmerman-11/12/03
KSrinivasachar-11/12/03
EMishina-11/12/03
FWilliams-11/12/03
TMarciniak-11/13/03
AKarkowsky-11/17/03
NStockbridge-11/18/03
DThrockmorton-11/19/03

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

/s/

Edward Fromm
11/19/03 02:33:13 PM
Dr. Throckmorton signed the minutes on November 19, 2003

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,596

Novadel Pharma Inc.
Attention: Mr. Paul S. Decker
Acting Director of Clinical and Regulatory Affairs
31 State Highway 12
Flemington, NJ 08822

Dear Mr. Decker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Lingual Spray.

We acknowledge receipt of your June 30, 2003, correspondence notifying us that your corporate name has been changed from

Flemington Pharmaceutical Corporation
31 State Highway 12
Flemington, New Jersey 08822

to

Novadel Pharma Inc.
31 State Highway 12
Flemington, NJ 08822

Our records have been revised to reflect this change.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

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Sincerely yours,

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Zelda McDonald
7/11/03 02:40:12 PM

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NovaDel Pharma Inc.
Novel Delivery of Pharmaceuticals

FAX

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

Retained copy + had one quarter.

Why are we 1st submitting ANDA rather than NDA?

301-554-5627

594-

June 16, 2004

USER FEE STATEMENT

In accordance with exclusions permitted for Section 505(b)(2) applications, as defined by the Food, Drug and Cosmetic (FD&C) Act, NDA 21-780, Aerosol Nitroglycerin Lingual Spray, 0.4 mg, submitted, herewith, by NovaDel Pharma Inc. fulfills the Agency's exclusion requirements.

NDA 21-780 Aerosol Nitroglycerin Lingual Spray is not a new molecular entity; nitroglycerin, which is the active ingredient, is not being submitted for approval of a new indication.

In keeping with the User Fee Exclusion requirements, while maintaining 505(b)(2) regulatory status, NovaDel submitted our proposed labeling on 5th June 2003 to Ms. Tawni Schwemer, CDER's User Fee Staff and a response was received back from Ms. Schwemer on the 16th July 2003 (correspondence attached) confirming our initial assumption that NovaDel's Nitroglycerin Lingual Spray would not be regarded as a fee-paying 505(b)(2) application.

In the interim, as discussions pertaining to labeling took place between NovaDel and the Cardio-Renal Drug Products Division during our pre-NDA Meeting of 4 November 2003, specific guidance was communicated to NovaDel regarding the Agency's requirements that, in constructing our 505(b)(2) application, we should specifically refrain from referring to proprietary data in any other sponsor's NDA and from merely copying the existing labeling of any other approved nitroglycerin product without independently supporting any statements in such labeling. Rather, we were instructed specifically to be certain to justify any statements that we might make in our proposed labeling with either our own data or information accessed from published literature.

Accordingly, wherever appropriate, NovaDel's product labeling is supported by data from clinical studies conducted by NovaDel Pharma Inc. and/or published findings from other sources, in accordance with conditions established during NovaDel's pre-NDA Meeting with FDA held on November 4, 2003.

We believe that the Agency will nonetheless be reassured that our proposed (current) labeling remains consistent with approved labeling for a similar nitroglycerin lingual spray product, Nitrolingual® Pumpspray (First Horizon Pharmaceutical Corporation) and the recently approved labeling for the sublingual nitroglycerin tablet Nitrostat® (Southward Pharmaceuticals, Inc, previously Parke-Davis' product). Important statements in NovaDel's proposed labeling approach the level typical for class labeling and reflect the current understanding of the mechanism of action and benefits and risks associated with nitroglycerin therapy for the acute relief and acute prophylaxis of anginal attacks.

Attachment

25 Minneakoning Road
Flemington
New Jersey 08822

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(908) 782-3431

Facsimile
(908) 782-2445

www.novadel.com

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

3 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Minutes of an Internal 30 Day Safety Meeting

Date: May 14, 2002

Application: IND 64,596
Nitroglycerin Lingual Spray (0.4 mg)

Sponsor: Flemington Pharmaceutical Co.

Participants:

Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
James Willard, Ph.D., HFD-110, Pharmacologist
Gabriel Robbie, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist, Acting Team Leader
Elena Mishina, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Edward Fromm, HFD-110, Regulatory Health Project Manager

Background

Flemington Pharmaceuticals has submitted Nitroglycerin Lingual Spray for the treatment of chronic stable angina. The sponsor's formulation

The sponsor plans on conducting a dose-ranging study that will enroll 30 patients in a double-blind, 4-way, crossover comparing 0.2 mg, 0.4 mg, and 0.8 mg nitroglycerin spray (per activation) versus placebo. In addition, a small pharmacokinetic (PK) study will be conducted in 10 patients to give an idea of blood levels after administration of a 0.4 mg dose.

CHEMISTRY - Dr. Stuart Zimmerman

Dr. Zimmerman said there were no CMC safety issues. He noted that potential of and other components of the formulation is a concern and therefore stability information for the product will be closely monitored. In addition, at this time, there are also no specifications on the particle size of nitroglycerin although the sponsor has committed to supplying a profile of the particle size in the future. Dr. Willard added that the labeling instructions for the currently market product (Nitrolingual Spray) indicate that the patient is not to breathe while inhaling so the nitroglycerin particles cannot be inhaled into the lungs.

PHARMACOLOGY - Dr. James Willard

Dr. Willard said that the butane propellant, in the concentrations that the sponsor proposed using, is within the limits of GRAS (Generally Recognized as Safe). He noted that butane has been abused an inhalant, may leave an aftertaste, and could be a fire hazard. Dr. Zimmerman mentioned that the sponsor had conducted tests that showed that there is no flammability hazard when the product was used more than a few centimeters from a flame as was indicated by the firm in a later conversation by telephone.

BIOPHARMACEUTICS - Dr. Elena Mishina

Dr. Mishina said there were no safety issues with the proposed studies. Dr. Robbie noted that that the proposed PK study would characterize the PK of nitroglycerin and its metabolites following a single dose of 1.2 mg which is administered as 3 actuations of 0.4 mg/actuation.. The PK of nitroglycerin and its metabolites could have been characterized for 3 doses following 1, 2 and 3 actuations using a crossover design given the short half-life of the parent drug and metabolites. This would aid in understanding the linearity of PK and consistency of delivery from the dosage form.

MEDICAL - Dr. Abraham Karkowsky

Dr. Karkowsky said that nitroglycerin products are generally safe and that, from a safety standpoint, the studies could proceed.

Conclusion

There are no clinical hold issues, and the study may proceed as planned.

Minutes Preparation: _____
Edward Fromm

Concurrence, Chair: _____
Abraham Karkowsky, M.D., Ph.D.

drafted: ef-5/22/02/6-17-02

Rd: SZimmerman-5-28-02
JWillard-5-31-02
EMishina-5-28-02
GRobbie-5-31-02

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/s/

Edward Fromm
6/17/02 02:38:56 PM
Dr. Karkowsky signed the minutes on June 17, 2002.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 64,596

Paul Decker
Flemington Pharmaceuticals Corporation
31 State Highway 12 West
Flemington, NJ 08822

Dear Sponsor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Lingual Spray 04MG.

We also refer to your submission dated 4/22/2002, serial number 000, containing information about a new protocol.

The purpose of this letter is to inform you about the Clinical Trials Data Bank available to the public through the Internet at http://clinicaltrials.gov. The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Food and Drug Modernization Act of 1997 (Modernization Act).

Section 113 of the Modernization Act amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). It directs the Secretary of Health and Human Services, acting through the Director of NIH, to establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions.

The Clinical Trials Data Bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases, other members of the public, healthcare providers, and researchers. Specifically, the Clinical Trials Data Bank will contain 1) information about clinical trials, both federally and privately funded, of experimental treatments for patients with serious or life-threatening diseases; 2) a description of the purpose of each experimental drug; 3) patient eligibility criteria; 4) the location of clinical trial sites, and 5) a point of contact for those wanting to enroll in the trial. This information must be submitted if the clinical trial concerns a serious or life-threatening disease or condition and if the trial tests effectiveness.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information about clinical trials for serious or life-threatening diseases or conditions to the Clinical Trials Data Bank.

The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions was made available on March 18, 2002. It is accessible through the Internet at http://www.fda.gov/cder/guidance/4856fnl.htm

The data fields and their definitions are available in the Protocol Registration System at http://prsinfo.clinicaltrials.gov/. Protocols listed in this system will be made available to the public on the Internet at http://clinicaltrials.gov.

Please review the referenced protocol to determine if it is a trial for a serious disease or condition and if it is a trial to test effectiveness. If the protocol meets these criteria, you must submit information about the trial to the Clinical Trials Data Bank, unless you provide detailed certification to FDA that such a disclosure would substantially interfere with the timely enrollment of subjects in the investigation (42 U.S.C. 282(j)(3) and (j)(4)). You can also submit information about clinical trials under IND that do not meet the criteria described in the Modernization Act.

We appreciate your cooperation. This project is a collaborative effort by the FDA Office of Special Health Issues, the FDA Center for Drug Evaluation and Research (CDER), and NLM/NIH. You will receive a similar letter for each new protocol submitted to a CDER IND during 2002. If you have any questions, contact Theresa Toigo or Janelle Ernat in the Office of Special Health Issues at (301) 827-4460 or e-mail at 113trials@oc.fda.gov.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

{See appended electronic signature page}

Theresa Toigo, RPh, MBA
Director
Office of Special Health Issues
Office of Communications and Constituent Relations
Office of the Commissioner

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/s/

Terry Toigo
6/7/02 05:08:51 PM

Deborah Henderson
6/11/02 11:28:40 AM
for Janet Woodcock, M.D.

Minutes of a Telecon between Flemington Pharmaceuticals and the FDA

Date: November 28, 2001

Sponsor: Flemington Pharmaceutical Corporation

Subject: Nitroglycerin Lingual Spray

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics, Team Leader
Gabriel Robbie, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Eleana Mishina, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Edward Fromm, HFD-110, Project Manager

Flemington Pharmaceutical Corporation

Dr. Harry Dugger, President and CEO

Background

Flemington Pharmaceuticals met with the Division on September 28, 1999 and April 27, 2000 to discuss the development of Nitroglycerin Lingual Spray for angina. They originally submitted this application as an ANDA to the Office of Generic Drugs but due to safety concerns regarding the butane propellant the submission was referred to the Cardio-Renal Division for review.

The sponsor requested a telecon to see if the descriptive PK study requirements outlined at the September 28, 1999 meeting could be changed or eliminated altogether.

Telecon

PK Studies

Dr. Dugger opened the telecon by noting that the Division (at the September 28, 1999 meeting) had requested descriptive PK data from at least 6 patients. Since that meeting, representatives from the Office of Clinical Pharmacology and Biopharmaceutics have suggested that PK data from at least 12 patients would better characterize the PK profile of the drug. Yet, from the sponsor's perspective, the data gained from 6 or 12 patients would yield very little clinically relevant information. Moreover, the assay is expensive with very few companies interested in analyzing the samples. Dr. Dugger asked if the labeling could use the current PK information listed with nitroglycerin products or if they could submit published references to support the PK section of the labeling.

Assuming a positive outcome from the dose-ranging study, Dr. Lipicky said the sponsor would need PK data in at least 6 patients so as to have some idea of the plasma concentrations achieved by the spray. If the PK information is not adequate due to the small sample size, additional PK data should be obtained post-approval.

Dose-Ranging Clinical Study

Dr. Robbie noted that the 0.2mg/0.4mg/0.8mg, and placebo doses, although agreed upon at the September 28, 1999 meeting, seemed too close together and asked if a [redacted] in the study. Dr. Dugger replied that headaches and other side effects would be more likely at that dose and would increase the risk of patient dropouts. Moreover, clinical samples of the 3 strengths have already been produced. Dr. Lipicky thought the adverse effects (headaches) from the [redacted] but said that the current protocol (0.2mg/0.4mg/0.8mg and placebo) was still acceptable.

Minutes Preparation:

Edward Fromm

Concurrence:

Raymond Lipicky, M.D.

dr/11-29-01

Rd: EMishina-11/30/01
GRobbie-11/30/01
PMarroum-11/30/01

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/s/

Edward Fromm
5/15/02 02:08:31 PM
CSO
Dr. Lipicky signed the minutes on December 12, 2001.

Edward Fromm
5/15/02 02:11:27 PM
CSO
Dr. Lipicky signed the minutes on December 12, 2001.

Minutes of a Meeting between Flemington Pharmaceuticals and the FDA

Date: April 27, 2000

Applicant: Flemington Pharmaceutical Corporation

Subject: Pre-IND Meeting (CMC)

FDA Participants:

Hasmukh Patel, Ph.D., Acting Deputy Director, Chemistry, Division of New Drug Chemistry I (HFD-810)
Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, Division of New Drug Chemistry I (HFD-810)
Joseph Piechocki, Ph.D., HFD-810, Chemist
Edward Fromm, HFD-110, Consumer Safety Officer

Flemington

Dr. Harry Dugger, President and CEO

Background

Flemington Pharmaceuticals met with the Division on September 28, 1999 to discuss the development of Nitroglycerin Lingual Spray for angina. The firm requested a meeting with the Division to go over CMC related issues regarding their proposed nitroglycerin spray product.

Meeting

Dr. Dugger opened the meeting by noting that the proposed nitroglycerin lingual spray was a homogenous solution and therefore might not have to undergo as extensive testing as other dosage forms (e.g., MDI's, oral suspensions). Dr. Dugger submitted a list (see attached) of areas he thought the lingual spray solution spray testing might require a different guidance for a NDA CMC section. FDA representatives then agreed to offer comments on the following sections of that list:

[redacted] studies

Dr. Piechocki noted that the [redacted] see USP test 381).

The firm asked if [redacted] could be used as solvents for the [redacted] studies. Dr. Piechocki said [redacted] were acceptable but that the firm could use [redacted] if modified appropriately. He also said that [redacted] did not have to be tested as an [redacted] solvent.

Valves

Dr. Piechocki referred the company to USP test ⟨661⟩; he said the firm should use that test to test the [redacted] components of the valve. Dr. Dugger said they were having supply problems with the valves for the nitroglycerin spray but believed [redacted] will be the [redacted] supplier. He added that this information would be supplied in the DMF when the NDA is submitted for the product.

Spray Content Uniformity (SCU)

Dr. Piechocki said this test needs to be done in quasi-use conditions. He said it was important to show that active/other formulation components, (e.g., [redacted] do not accumulate at the tube exit. Dr. Dugger said they were proposing to test the spray in solution. Dr. Piechocki suggested that the firm do a one-time [redacted] test with the spray to confirm the equality of the two procedures.

Dr. Dugger asked the FDA participants if the company could use the [redacted] Method to determine the amount released per activation. Dr. Srinivasachar noted that the [redacted] Method was specific for tablets and capsules. Dr. Piechocki said it would be acceptable to collect 10 spray samples from each of 10 bottles and do an average of the 10 samples per bottle and 10 bottles. Dr. Srinivasachar said, however, that the firm would have to show equivalence between the method they choose to use for weight per activation and the Assay method.

SCU Through Container Life

Dr. Piechocki said a one-time test through the life of the container would be sufficient to test for the active concentration of the drug, barring leakage or degradation.

Identification of the Drug Substance

Dr. Piechocki said it would be helpful for the firm to conduct another test, such as HPLC, before final release of the product.

Container Storage Orientation

Dr. Piechocki noted that [redacted]. He said it was not necessary to do the tests with the container on the side. Dr. Patel noted that testing of the bottles in inverted and upright positions would be required for an NDA submission.

Priming/Repriming in various orientations

Dr. Piechocki said that instructions for priming should appear in the labeling for the product. He said the firm should also conduct a [redacted]

Temperature Cycling

Dr. Piechocki noted that the firm should conduct a [redacted]

Effect of varying flow rates

Dr. Piechocki mentioned that varying flow rates should not be an issue with this product.

Profiling of Sprays near container exhaustion

Dr. Piechocki said the firm would need an assay; he noted it was acceptable to do this on a weight basis. It would be necessary when doing the test to take measurements at the beginning, mid-way, and end to show that the homogeneity did not change throughout the entire spray period.

Photostability

Dr. Dugger said [redacted] but said that testing done so far has found no degradants. Dr Piechocki said that if [redacted]

IND, NDA submission

Dr. Srinivasachar asked when the company plans to submit an IND for the nitroglycerin spray? Dr. Dugger said Flemington would submit an IND in August of this year and would submit an NDA sometime in 2001.

Conclusion

Dr. Piechocki said the Division was willing to discuss at any time CMC issues that arise during the development of this product.

Minutes Preparation: _____
Edward Fromm

Concurrence Chair: _____
Hasmukh Patel, Ph.D.

ef/5-11-00/5-19-00/5-23-00

Rd: JPiechocki-5/12/00
KSrinivasachar-5/17/00

cc: HFD-110
HFD-110/EFromm/SMatthews

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/s/

Edward Fromm
5/15/02 02:01:17 PM
Dr. Patel signed the minutes on May 23, 2000.

Minutes of a Pre-IND Meeting

Date: September 28, 1999

Sponsor: Flemington Pharmaceutical Corporation

Subject: Nitroglycerin Lingual Spray

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Shaw Chen, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Elizabeth Hausner, D.V.M., HFD-110, Pharmacologist
Joseph Piechocki, Ph.D., HFD-810, Chemist
Emmanuel Fadiran, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
James Hung, Ph.D., HFD-110, Statistical Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Consumer Safety Officer

Flemington Pharmaceutical Corporation

Dr. Harry Dugger, President and CEO
Dr. Donald P. Cox, Vice President, Research and Development

[redacted]

Background

Flemington Pharmaceuticals met with the Division on September 28, 1999 to discuss the development of Nitroglycerin Lingual Spray for angina. The firm originally submitted this application as an [redacted] but due to safety concerns regarding the butane propellant the submission was referred to the Cardio-Renal Division for review.

Meeting

Chemistry, Manufacturing and Controls (CMC)

Dr. Piechocki passed out a handout (appended to these minutes) to the members of the firm outlining possible deficiencies with their plans to develop the Nitroglycerin Lingual Spray. The Division's concerns are as follows:

1. [redacted]

   that in their tests only [redacted] Dr. Lipicky was concerned that if this product were shipped in mass quantity throughout the country that the explosion risks would be much greater, especially because the propellant is to be butane. He

noted that the firm would need to document that the ' [redacted] is not explosive. He added that the safety data should also indicate that the product is not hazardous to people who may use the drug around open flames or glowing embers.

2. The Division recommended that the firm follow MDI (metered dose inhaler) guidelines where applicable and if this is not possible the firm will need to document why they should be exempted.

3. Dr. Piechocki asked the firm to do the [redacted] Test for the [redacted].

4. Dr. Piechocki noted that the spray sampling method did not meet USP standards. He added that another method could be used but it would have to be equal to or better than the USP's.

5. Nitroglycerin per spray content method. Dr. Piechocki was concerned that the firm may be including spray around the [redacted] in its measurement of total spray released per actuation.

6. Photostability Test. Dr. Piechocki recommended that the initial testing be done with the GTN (glycerol trinitrate) and [redacted] mixture. If the mixture tested favorably the company could then end the photostability testing.

Clinical

Dr. Lipicky outlined two approaches that Flemington could take in designing efficacy studies for the Nitroglycerin Lingual Spray:

1. Bioequivalence studies (i.e., two actuations of the drug give higher plasma levels than 1 actuation). The main detriment to this type of study is that several hundred or more patients would be needed and even then it might not be easy to declare bioequivalence.

2. Dr. Lipicky preferred a study using exercise tolerance tests, showing dose-response and a positive slope. He recommended a single trial, parallel design, and that the patients enrolled in the study could be nitrate responders. He added that comparison with nitroglycerin sublingual tablets is unnecessary. He noted that there should be at least four arms to the study (3 doses-0.2mg/0.4mg/0.8mg and placebo) and that there should be at least 30-40 patients per arm. The firm asked if a crossover design could be used with fewer patients. Dr. Lipicky stated that they could take this approach but if there were dropouts it could seriously jeopardize the outcome of the study. He did indicate that the duration of the trial could be similar to that taken by Dr. Parker in his studies with nitroglycerin spray. Dr. Lawrence mentioned that the trial can be blinded by using multiple bottles-some of which contain inactive ingredients. Dr. Piechocki noted that the patients in the trial should not have their mouth dried before using the spray.

The firm asked the Division if pharmacokinetic studies would be needed for this product. Dr. Lipicky stated that descriptive PK data would be needed although the results of as few as six patients could be used to support that section of the application.

505(b)(2) status

The firm hopes eventually to submit the Nitroglycerin Lingual Spray as a 505(b)(2) NDA. The firm was reminded that it would be required to submit the appropriate patent certification (see 21 CFR 314.52).

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Raymond Lipicky, M.D.

dr/9-29-99/10-8-99

Rd: JPiechocki/10-4-99
EFadiran/10-4-99
JLawrence/10-4-99
JHung/10-4-99
EHausner/10-5-99
MGordon/10-5-99
SChen/10-5-99
NMorgenstern/10-7-99

cc: Orig.
HFD-110
HFD-110/Blount
HFD-110/EFromm/SMatthews

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/s/

Edward Fromm
5/15/02 01:51:52 PM
Dr. Lipicky signed the minutes on October 8, 1999.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,596

Flemington Pharmaceutical Corporation
Attention: Mr. Paul Decker
31 State Highway 12 West
Flemington, N.J. 08822

Dear Mr. Decker:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 64,596

Sponsor: Flemington Pharmaceutical Corporation

Name of Drug: Nitroglycerin Lingual Spray(0.4mg)

Date of Submission: April 22, 2002

Date of Receipt: April 23, 2002

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before May 23, 2002, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call me at (301) 594-5313.

Sincerely yours,

Edward Fromm
Regulatory Project Manager
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
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