CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-780

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-780

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 and received August 4, 2004 (date removed from Arrears List), submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for NitroMist™ (Nitroglycerin Lingual Aerosol) 400 mcg/actuation.

We acknowledge receipt of your submissions dated June 25, July 6, 7, 15, 29 (two), and 30 (two), August 4, 6 (two), 12, October 26, November 5, 15, December 6, 20, 2004 and January 11, 27, February 11, March 24, 30, April 15, May 3, 16, 17 and 20, 2005.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following issues:

CHEMISTRY

DMF Issues:

1. DMFs [redacted] and [redacted] cited in support of your NDA have deficiencies that have been conveyed to the respective DMF holders.

Drug Substance:

1. Propose a short holding time for your GTN Basic Solution since data from formal stability studies for this non-compendial formulation have not been provided.

Drug Product:

1. Confirm the validity of your content uniformity sampling approach (i.e., using [redacted] testing regimes) and conduct comparative testing that includes a [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 set (e.g. % RSDs).
2. Provide GTN priming data to support your initial claim in the labeling that priming twice after an inactive period of [redacted] weeks is sufficient to assure consistent dosing since more

recent studies in your amendment of 2/11/05 suggest additional priming is required to achieve the label claim for GTN content even after shorter inactive intervals.

3. Submit release data for validation batches or site specific stability data to support the use of INyX, PR as the commercial manufacturing site.
4. Provide test procedures and validation data for HPLC methods [redacted] and [redacted] and incorporate them into drug product specifications, stability protocols, and specifications for GTN Basic Solution as appropriate. Note that [redacted] is a regulatory method which should be used for the release of every batch of drug product as well as stability testing.
5. Provide complete details of the [redacted] method (v.2, p. 88) for the valve components, clarify if you perform this test on every batch and interpret the results in terms of safety considerations. Explain why the part numbers are different from those cited in the LOAs from [redacted]
6. Your proposed addition of [redacted] as an alternate microbiological testing site cannot be reviewed at this time since it was just recently submitted. For your proposal to use another alternative testing site, it should be identified by name and by specific testing function to allow appropriate review.

Please note that we have attached our revised labeling and request the following additional labeling revisions:

1. Provide bottle and carton labels revised as follows:
   (a) Delete the word '[redacted]' from the label.
   (b) Relocate the established name so that it appears directly underneath the proprietary name. Additionally, revise the established name so that it is at least half as large as the letters comprising the proprietary name in accordance with 21 CFR 201.10(g)(2).
   (c) Relocate the net quantity so that it does not appear in close proximity to the product strength.
   (d) Include priming/re-priming directions for patient use in accord with the outcome of your studies.
   (e) Make your storage statement consistent with your revised P.I.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Cardio-Renal Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Enclosure:

8 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Norman Stockbridge
5/31/05 04:57:33 PM