DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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JUN 27, 1997

WARNING LETTER

Mr. Jacques Messier
President & Chief Operating Officer
Novopharm Ltd.
30 Nably Court
Scarborough, Ontario, Canada M1B 2K9

Re:		
	A) 30 Nably Court	CFN 9611985
	B) 50 Nably Court	CFN 9611985
	C) 1276-90 Ellesmere Rd.	CFN 9690069
	D) 5691 Main Street	CFN 9613479
	E) 575 Hood Road	CFN 9690072

Dear Mr. Messier:

FDA has completed its review of the inspection of the five oral solid dosage manufacturing facilities identified above, in Ontario, Canada by Investigator Anthony Warchut and Analyst Azza Talaat in February/March 1997 and your April 24, 1997 response. The inspections revealed significant deviations from current good manufacturing practices (CGMP) in the manufacturing of oral solid dosage pharmaceuticals. The deviations were presented to your attention on the FDA-483s, Lists of Observations at the close of

The specific areas of concern include, but are not limited to the following:

1. Process validation procedures do not provide a high degree of assurance that the process will consistently produce in-specification product. The process for Atenolol tablets was validated/revalidated three times since July 1992 because of problems with moisture, blend uniformity, and dissolution. These problems should have been resolved during development, prior to validation (A. FDA-483 Item # 2-3, 5-6).

2. Investigations of out-of-specification blend uniformity results during the Atenolol validation studies were inadequate to assure the adequacy of mixing (A. FDA-483 Item #3-4).

3. Laboratory investigation of out-of-specification dissolution results during the Atenolol validation studies improperly averaged out-of-specification results with in-specification results to obtain a passing average (A. FDA-483 Item #5).

4. In-process manufacturing problems were not adequately investigated or evaluated by the Quality Control Unit (A. FDA-483 Item #9-11).

5. Documentation of development and scale-up activities were inadequate (B. FDA-483 Item #2-4; D. FDA-483 Item #1,7,10; and E. FDA-483 Item #1-3, 7).

6. Analytical methods were not adequately validated (D. FDA-483 Item #7; E. FDA-483 Item #8).

7. The change control system was inadequate in that no evaluation of the effect of vendor changes on Tolmentin capsules was initiated (C. FDA-483 Item #4-5).

8. Equipment calibration is not adequate for the apparatus (D. FDA-483 Item #3).

The April 24, 1997 responses appear to provide satisfactory corrective actions for specific products and appropriate new or revised SOPs to address recurrence of these deficiencies. They do not adequately address these same deficiencies as they relate to the product development and scale-up procedures for other products with pending applications which have not yet been inspected, nor validation procedures for other approved products which are being shipped to the U.S. Previous inspections have revealed similar deficiencies where corrections were implemented, but may not have been applied to all products and processes. Some of the deficiencies observed during this inspection may have occurred prior to those corrective actions, but it appears that the corrective action did not include a retrospective review of previous development, scale-up, and validation activities.

VALIDATION

Validation is defined as "established documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined

specifications". As such, specifications and limits should be developed prior to reaching the process validation stage.

Once a specific manufacturing process has been validated, it should remain in control unless changes have been made to the process which warrant a re-validation. Process parameters should be developed during the research and development stage, then verified at the time of process validation. Process parameters should not be developed during validation as was done with Atenolol tablets.

Your validation reports for this product indicate a number of batches which were intended for process validation but were subsequently discontinued because of various problems with moisture parameters and blend uniformity. These problems appear to be due to insufficient research and development data. Validation data is insufficient to provide a high degree of assurance that the process will consistently produce a product meeting all specifications.

The investigation into out-of-specification blend uniformity results for Atenolol tablets was inadequate in that it did not evaluate whether or not the blender used during the second validation plan was the cause of the failure. The investigation concluded that sample handling procedures (bottles and labels) caused the failure. It did not address whether or not the same bottles and labels were found acceptable for the previous validation.

The investigation for Atenolol lot concluded that the duplicate samples taken were found acceptable with the exception of the end sample for the lot. This conclusion did not mention that the duplicate samples were left at ambient conditions for two days and therefore treated differently than the original set of samples.

It is unclear from your investigation if any "dead spots" have been identified in your These areas tend to be where active ingredient or other parts of a formulation adhere to contact surfaces, and may have been a cause for the out-of-specification result.

The Atenolol validation studies are also inconsistent as the scrapings were added back to the blender during the first validation while they were discarded during the second validation. The second validation revealed a uniformity problem in the end sample result. The method of correction was to discard the blender tailings. Since subpotent results from one area of a blend may cause superpotency in other areas, this action does not assure adequacy of mixing. In addition, the three validation batches were not manufactured according to the

same process. The process validation report concludes that once discarding the tailings resulted in acceptable end samples, the procedure was validated. This is not an acceptable conclusion as it is based on one batch which was different from previous validation where the tailings were added back to the granulation.

Please provide information and supporting documentation that the procedure to discard scrapings results in uniformity of the remaining granulation.

Your response commits to manufacturing one scale-up batch and re-validating the manufacturing process for Atenolol tablets. This action appears to address our concerns with this and future products, but we are also concerned about the process validation for other products manufactured and shipped to the United States. According to information provided, ten approved products are currently being shipped to the U.S. We recommend that the process validation studies for these products be reviewed and request assurance that the same type of deficiencies did not occur during validation studies, or have been corrected with supplemental studies.

PROCESS DEVELOPMENT

The inspections disclosed insufficient documentation of product development and process scale-up activities for the products covered during the inspection. Although the responses commit to updating and or evaluating and improving existing procedures, this is only part of the solution. The responses do not address what corrective actions will be taken regarding other products currently pending approval. We are concerned that similar deficiencies regarding other products will be found because these observations suggest systematic and global deficiencies in your process development procedures.

Please describe in your response what global corrective actions will be initiated regarding other pending ANDA's which have not been inspected.

INVESTIGATIONS

Inadequate investigations of non-conforming results and in some instances, no investigation into a problem (A. FDA-483 Items #9-11) were observed. When problems with the manufacturing process occur, there is no assurance that the Quality Control Unit evaluates the issues and corrective action(s). For example, part of a batch of Atenolol was rejected due to the presence of "string" in the granulation (A. FDA-483 Item #9a). There

appeared to be no formal investigation as to how or why the string was in the granulation. The corrective action included screening the granulation as part of the manufacturing process without an evaluation of the effect of using . The amount of rejected granulation was subsequently included within yield reconciliation as an acceptable loss. This loss was or approximately tablets. No further action to preclude recurrence of the problem was taken.

In another example, a tablet was found by production personnel in the granulation hopper (A. FDA-483 Item #11). The granulation was screened from the hopper and production was resumed. There was no investigation of the cause for this problem. The response did not address whether or not this was the same product tablet, whether or not the tableting equipment had been improperly set-up, or other issues which may have been the cause. The Quality Control Unit was not notified of the problem.

LABORATORY PROCEDURES

During the validation studies for Atenolol tablets, S_1 failing dissolution results from one bottle were averaged with the initial S_1 passing results from another bottle; rather than testing an additional six tablets of the same bottle at the S_2 level as required by the USP method (A. FDA-483 Item #5). This is not acceptable. Your response only addresses future process validation protocols. It does not address the evaluation of other dissolution and other analytical out-of-specification results, both past and future, or training of laboratory personnel in USP methods and good laboratory procedures.

We recommend that you review other laboratory results to assure that passing and failing results were not and are not averaged to obtain a passing result for other approved products currently shipped to the U.S.

The inspection revealed an HPLC impurities method was not validated for accuracy (E. FDA-483 Item #8). The response indicates that an additional study was performed in which a batch of tableted product was spiked with a known amount of impurities and your recovery was found to be acceptable. The study also concluded that the low recovery was "reasonable and acceptable considering the low amount of impurity spiked into the sample". Typically, accuracy for impurities is performed on the active ingredient since the tablet product includes inactive ingredients which may interfere with recovery.

Please explain why this study was performed on tablets and how the study was conducted. Please also provide assurance that other analytical methods have been adequately validated.

The inspections also revealed that robustness was not included as part of the method validation of the HPLC assay and dissolution test method (D. FDA-483 Item #7). Although the response was acceptable, we disagree with your interpretation of robustness. USP 23, under section <1225> defines robustness as "...a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of reliability during normal usage". Your response stated that the robustness of your assay method was assured by the tight system suitability specification incorporated into the method. This does not meet the definition of robustness.

System suitability testing is performed on a standard while the robustness of a method is typically performed on the product to be tested. System suitability will provide information regarding the system at that particular time but does not address the undetected but deliberate variations in a method.

According to your response to the A. FDA-483 Item #1, your firm conducted an investigation into the number of occurrences where the S_2 level was reached due to failing S_1 levels for dissolution. The response lists the following lots as completed at stage 1, however 12 units of each lot were tested for dissolution. Please explain this discrepancy and include copies of raw data to support your response.

* This lot includes a comment which states "No action required, all lots conform to S1".

Our review has indicated that the Atenolol tablet dissolution method currently being used is the UV method which was approved in your application. Atenolol Tablets has recently been included in the USP, therefore the USP method, which is an HPLC analysis, is now the official test method for this product.

The inspection revealed the apparatus had not been standardized prior to each analysis (D. FDA-483 Item #3). The response to this deficiency is inadequate as it addresses the standardization of the reagent, and not the calibration of the equipment. Please include in your written response, the action

taken to assure that the apparatus will be calibrated prior to each analysis.

CHANGE CONTROL

The inspection revealed an inadequate change control system, as vendor changes did not prompt the issuance of a change control request as was demonstrated with Tolmentin capsules, (C. FDA-483 Item #4-5). The response commits to evaluating the Non-conformance Materials Report system and change control.

To ensure a continued state of process control, the FDA expects manufacturers to establish a formal change control system to evaluate all changes that may affect the production and control of finished drug products. These written procedures should provide for the identification, documentation, appropriate Q.C. review and approval of both anticipated and unanticipated changes in components, facilities, support systems, equipment, processing steps, and packaging materials. The evaluation should determine if and to what extent validation is needed and specify additional testing (i.e. stability studies etc.) which will be conducted to evaluate the potential impact of any changes on the finished drug product.

Please include in your written response the results of the evaluation your firm has conducted concerning what actions will be taken for non-conforming, out of specification issues which may arise during the manufacture of finished pharmaceuticals.

The CGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your facilities. FDA inspections are audits which are not intended to determine all deviations from CGMPs that exist at a firm.

Based upon the global and systematic CGMP deficiencies observed during the inspections of your various sites, we recommend that you evaluate these facilities on an overall basis for CGMP compliance. If you wish to continue to ship your products to the United States, it is your responsibility of to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers. An evaluation should also be conducted for all products currently shipped to the United States.

Until FDA has confirmed that these facilities are in CGMP compliance, we will not recommend approval of any applications for finished drug products manufactured by 30 & 50 Nabfy Court as well as 1276 & 1290 Ellesmere Road facilities.

Please contact Compliance Officer Patricia L. Alcock, [telephone: (301) 594-0054; fax: (301) 594-2202] of this division at the above address if you have any questions. Within your written response to this letter, detail corrective actions you plan to take or have taken to bring your operations into compliance. Please include a timetable of when each of the corrections will be completed and attach supporting documents.

To schedule a reinspection of these facilities, after corrections have demonstrated CGMP compliance, send your request to: Dr. Attila Kadar, Consumer Safety Officer, Division of Emergency and Investigational Operations (HFC-134), 5600 Fisher's Lane, Rockville, MD 20857. You can contact that office by telephone at (301)827-5653 or by fax at (301) 443-6919.

To assist in planning this reinspection, please provide a list of pending applications and a list of approved products shipped to the U.S., and identify their manufacturing and testing sites.

Sincerely,

Douglas I. Ellsworth
Director
Division of Manufacturing and
Product Quality, HFD-320

cc:

David Wong, Ph.D.
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30 Nably Court
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