CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-642

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

6. ***Submit a signed copy of the Paragraph IV patent certification.***

Paragraph IV Patent Certification under 21 CFR 314.50

Applicant declares as follows:

To the best of Applicants' knowledge there has been only one patent submitted with NDA 19-722 relating to the listed drug in gel form, that is U.S. Patent No. 4,724,231. Applicant certifies that Applicant has a license to U.S. Patent No. 4,724,231, from Questcor Pharmaceuticals, Inc. the owner of the patent and the NDA holder, for among other things, to pursue approval of this application.

Steven C. Quay,
Chairman, President, and CEO
Nastech Pharmaceutical Company, Inc.

24 March 2004
Date

7. ***Submit Form FDA 3542a (7/03).***

Please see Attachment III.

8. ***Submit a signed certification that the patent holder has been notified that the application has been filed and documentation that the patent holder received the notification.***

Please see Attachment IV.

9. ***Submit a signed statement that Nastech Pharmaceutical Company, Inc. has a licensing agreement with the patent owner.***

Please see Attachment IV.

10. ***Submit a signed statement from the patent owner that it consents to an immediate effective date upon approval of this application.***

Please see Attachment IV.

Attachment III

FDA Form 3542a

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

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

NDA NUMBER
21-642

NAME OF APPLICANT / NDA HOLDER
Nastech Pharmaceutical Company, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)
Nascobal (cyanocobalamin nasal spray)

ACTIVE INGREDIENT(S)	STRENGTH(S)
cyanocobalamin	500 mcg/0.1mL

DOSAGE FORM
Nasal Spray

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

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

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

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

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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

2. Drug Substance (Active Ingredient)

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

Drug Product (Composition/Formulation)

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

4. Method of Use

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

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

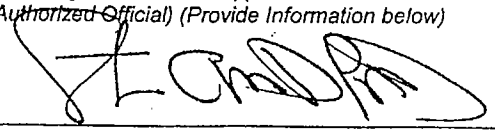
5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	3/24/2004

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

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Dr. Steven Quay, Chairman, President, and CEO, Nastech Pharmaceutical Company, Inc.

Address	City/State
3450 Monte Villa Pkwy	Bothell, WA
ZIP Code 98027	Telephone Number 425-908-3640
FAX Number *(if available)* 425-908-3655	E-Mail Address *(if available)*

Attachment IV

Supporting Documents for Questions 8, 9, and 10

Signed Statements Regarding Patent Notification, Licensing Agreement, and Immediate Effective Date

QUESTCOR

Gordon Brandt, MD
Executive Vice President Clinical Research & Medical Affairs
Nastech Pharmaceutical Company, Inc.
3450 Monte Villa Parkway
Bothell, WA 98021

March 19, 2004

Re: Patent-related issues related to NDA 21-642 as set forth in FDA Request on 01 March 2004

To fulfill the requests in items 8, 9, and 10 of FDA's 01Mar2004 communication regarding the patent referenced in NDA 21-642, Questcor Pharmaceuticals, Inc. hereby certifies that:

it is the patent holder of U.S. Patent No. 4,724,231, and has been notified by Nastech Pharmaceutical Company, Inc. that NDA application 21-642, which references U.S. Patent No. 4,724,231, has been filed. This statement is documentation that the patent holder has received the notification;

Nastech Pharmaceutical Company, Inc. has a licensing agreement with the patent owner, Questcor Pharmaceuticals, Inc; and

the patent owner, Questcor Pharmaceuticals, Inc., consents to an immediate effective date upon approval of NDA application 21-642.

Very truly yours,

David J. Dempsey

David J. Dempsey
Sr. Director, Regulatory Affairs & Quality Assurance
Questcor Pharmaceuticals, Inc.
3260 Whipple Road
Union City, California 94587-1217
ddempsey@questcor.com
(510) 400-0749
(510) 400-0775 (fax)

Paragraph IV Patent Certification under 21 CFR 314.50(c)(i)(4)(B)(3)

Applicant declares as follows:

To the best of Applicants' knowledge there has been only one patent submitted with the NDA of the listed drug, that is U.S. Patent No. 4,724,231. Applicant certifies that Applicant is the assignee to said patent and thus owns all rights to said patent and is fully free to practice the claimed invention of the patent.

NDA 21-642
10-25-04

EXCLUSIVITY SUMMARY FOR NDA # **21-642**

Trade Name **Nascobal Nasal Spray** Generic Name **cyanocobalamin**

Applicant Name **Nastech Pharmaceutical Co. Inc.** HFD # **510**

Approval Date If Known **Application will be AE 10/29/04**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /**XX**/ NO /___/

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

505(b)(2)

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

YES /___/ NO /**XX**/

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

This application is for a new dosage form, a change from an intranasal gel to an intranasal spray. This study is needed to demonstrate bioequivalence.

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

Not Applicable

d) Did the applicant request exclusivity?

YES /___/ NO /**XX**/

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

_____

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

YES /___/ NO /**XX**/

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

_____

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

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

YES /___/ NO /___/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

an already approved active moiety.

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or

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

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

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

---

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

YES /___/ NO /___/

If yes, explain:

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

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

section.

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

Signature: Holly Wieland, RN, MPH Date: October 19, 2004
Title: Regulatory Project Manager
Division: DMEDP-HFD-510

Signature: Mary Parks, MD
Title: Deputy Division Director Date:
Division: DMEDP-HFD-510

Form OGD-011347 Revised 05/10/2004

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

/s/

Mary Parks
10/25/04 12:19:31 PM

10/21/04

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : NDA 21-642

Stamp Date: December 26, 2003 Action Date: October 29, 2004

HFD 510 Trade and generic names/dosage form: Nascobal Nasal spray (cyanocobalamin)

Applicant: Nastech Pharmaceuticals company Inc. Therapeutic Class: 3

Indication(s) previously approved. None

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

Number of indications for this application(s): 1

Indication #1: : Maintenance of normal hematologic status of pernicious anemia patients

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

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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

This page was completed by:

Holly Wieland, RN, MPH
Regulatory Project Manager
DMEDP-HFD-510
CDER

{See appended electronic signature page}

cc: **NDA 21-642**
HFD-960/ Grace Carmouze

(revised 12-22-03)

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

/s/

Holly Wieland
10/21/04 02:47:42 PM

NASTECH
PHARMACEUTICAL COMPANY INC.

Corporate Headquarters
3450 Monte Villa Parkway
Bothell, WA 98021
Tel: (425) 908-3600
Fax: (425) 908-3650
www.nastech.com

45 Davids Drive
Hauppauge, NY 11788
Tel: (631) 273-0101
Fax: (631) 273-2469

420 Lexington Avenue
Suite 300
New York, NY 10170
Tel: (212) 297-6191
Fax: (212) 479-2554

November 10, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Drug Products, HFD-510
5600 Fishers Lane
Rockville, MD 20857

Re: Nascobal (Cyanocobalamin, USP) Nasal Spray
NDA #21-642
Debarment Certification Statement

To Whom It May Concern:

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

Sincerely,

Peter C. Aprile, R.Ph.
Vice President
Regulatory & Quality Affairs

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-642	Efficacy Supplement Type SE-	Supplement Number	
Drug: Nascobal (Cyanocobalamin, USP) Spray for Intranasal Administration		Applicant: Nastech Pharmaceutical Company, Inc.	
RPM: Holly Wieland, RN, MPH		HFD-510	Phone # 301-827-6410
Application Type: ( ) 505(b)(1) **(X)** 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 19-722 Nascobal Intranasal Gel	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	February 2, 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	**(X)** Paid UF# 4528
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ 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)	
• OC clearance for approval	
❖ 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.	**(X)**
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III **(X)** IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	**(X)**

❖ Exclusivity (approvals only)	
• Exclusivity summary	10/25/04
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	02/24/04, 03/09/04
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE letter 10/28/04
• 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	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	01/20/05
• Original applicant-proposed labeling	12/26/03
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	08/04/04 DMETS Consult Complete
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	12/01/04
• Reviews	01/26/05
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**Included**
❖ Memoranda and Telecons	11/19/04 & 11/22/04
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	11/01/01
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA
❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA

❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)	NA
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	10/19/04, 01/19/05
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	NA
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	10/21/04
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	NA
❖ Biopharmaceutical review(s) *(indicate date for each review)*	10/01/04 BP Review 10/06/04 BP Addendum 01/19/05 BP Review
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	03/10/03 DSI Consult Sent 06/30/04 DSI Response 09/17/04 DSI Addendum
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	02/25/04 Acceptable for filing 08/20/04 DMF Review 10/08/04 Review-AE recommended 01/26/05 Review-AP recommended
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	10/08/04
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	10/08/04
❖ Facilities inspection (provide EER report)	Date completed: 01/12/05 **(X)** Acceptable
❖ Methods validation	**(X)** Completed
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	02/09/04 Acceptable for filing 06/28/04 Approval recommended
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

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/s/

Holly Wieland
2/1/05 08:46:41 AM

01/31/05

Division of Metabolic and Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-642

Name of Drug: Nascobal (cyanocobalamin) Nasal Spray

Applicant: Nastech Pharmaceutical Company Inc.

Material Reviewed:

	Product Identifier	Rev. Date	Submission Date:
Package Insert:	#3065	01/05	01/20/05
Container Label:	#3064	11/04	12/01/04
Carton Label:	#2062	11/04	12/01/04

Background and Summary

The sponsor submitted this application, NDA 21-642, as a 505 (b)(1) application with full right of reference to NDA 19-722, Nascobal (cyanocobalamin) Gel, approved November 5, 1996. However, NDA 19-722 has been reassessed as a 505(b)(2) because it did not provide full clinical and preclinical studies. This application for Nascobal Nasal Spray relies on a bioequivalence study that compared the nasal spray to the nasal gel.

The active ingredient, cyanocobalamin, and the strength of the active ingredient per dose, 500 mcg/0.1 mL, were identical.

The biopharmaceutical reviewers found that after correcting for baseline values, the intranasal spray was 10% less bioavailable than the intranasal gel. This product is also less bioavailable than the intramuscular formulation. Since this product cannot be considered bioequivalent to the reference listed product, clinical use of this product or any cyanocobalamin formulation would require close monitoring of vitamin B_{12} levels and patients not achieving adequate vitamin B_{12} levels will require increased dosing with subsequent blood monitoring.

To address these bioequivalence differences, the company was advised in an approvable letter dated September 29, 2004, to revise the package insert (PI) to include a discussion of the difference in pharmacokinetics of the two intranasal products and advice that patients treated with the nasal spray should have vitamin B_{12} levels closely monitored with dose amount and/or frequency adjusted to achieve adequate levels.

To improve consistency with labels, the company was advised to change "room temperature" to "controlled room temperature" on the carton and container labels.

Review

Package Insert

The sponsor was advised on January 19, 2005, by telephone of the required labeling changes to its December 1, 2004, labeling in the PHARMACOKINETICS absorption section and in the DOSAGE AND ADMINISTRATION section. The changes requested are listed below.

Under PHARMACOKINETICS:
Delete the following text.

Add the following text. "A 3-way crossover study in 25 fasting healthy subjects was conducted to compare the bioavailability of the B12 nasal spray to the B12 nasal gel and to evaluate the relative bioavailability of the nasal formulations as compared to the intramuscular injection. The peak concentrations after administration of intranasal spray were reached in 1.25 ± 1.9 hours. The average peak concentration of B12 obtained after baseline correction following administration of intranasal spray was 757.96 ± 532.17 pg/ml. The bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%. The bioavailability of B12 nasal spray was found to be 10% less than the B12 nasal gel. The 90% confidence intervals for the loge –transformed AUC(0-t) and Cmax was 71.71%-114.19% and 71.6%-118.66% respectively."

Add the word, "gel" in the following sentence. "In pernicious anemia patients, once weekly intranasal dosing with 500 mcg B12 **gel** resulted in a consistent increase in pre-dose serum B12 levels during one month of treatment ($p < 0.003$) above that seen one month after 100 mcg intramuscular dose (Figure)."

Delete the following text.

Under DOSAGE AND ADMINISTRATION:
The sponsor added a final sentence to the paragraph beginning, "The recommended initial dose..." The additional sentence states, "Periodic monitoring of serum B_{12} levels should be obtained to establish adequacy of therapy."

The sponsor has complied with all requested changes in its January 20, 2005, submission.

The Medical Officer, Biopharmaceutical Reviewer and Chemistry Reviewers have found these revisions acceptable.

Carton Label
The word "controlled" has been added to the storage conditions and the revision date has been changed to 11/04.

The Chemistry Reviewer finds these changes acceptable.

Container Label
The word "controlled" has been added to the storage conditions and the revision date has been changed to 11/04.

The Chemistry Reviewer finds these changes acceptable.

Conclusions

The revisions are acceptable and an approval letter should be sent. FPL should be requested. The acceptable draft labeling is listed:

- Package Insert: Product Identifier #3065 Rev. Date 01/05
- Container Label: Product Identifier #3064; Rev. Date 11/04
- Carton Label: Product Identifier #2062 Rev. Date 11/04

Holly Wieland, RN, MPH
Regulatory Project Manager
DMEDP, HFD-510

Supervisory Comment/Concurrence:

Enid Galliers,
Chief, Project Management Staff

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/s/

Holly Wieland
1/31/05 03:33:09 PM
CSO

1/25/05

MEMORANDUM OF T-CON MEETING MINUTES

MEETING DATE: November 19, 2004
TIME: 9:30 a.m.
LOCATION: DMEDP, HFD-510 Room 14B04
APPLICATION: NDA 21-642
DRUG NAME: Nascobal Nasal Spray
TYPE OF MEETING: End of Review Meeting
MEETING CHAIR: Mary Parks, MD

MEETING RECORDER: Holly Wieland, RPM

FDA ATTENDEES:
Mary Parks, MD
Hae Young Ahn, PhD
Jayabharathi Vaidyanathan, PhD
Enid Galliers, CPMS
Holly Wieland, RPM

EXTERNAL CONSTITUENT ATTENDEES:
Nastech Pharmaceutical Company, Inc.
Gordon Brandt, MD, Executive Vice President of Medical Affairs
Anthony Sileno, Senior Director of Toxicology and Clinical Trials

Questcor Pharmaceuticals, Inc.
Reinhard Koening, MD, Vice President of Medical Affairs
David Dempsey, Senior Director of Regulatory Affairs and Quality Assurance

BACKGROUND:
Nastech Pharmaceutical Company received an approvable letter issued on October 28, 2004, that identified clinical/biopharmaceutical and regulatory deficiencies in the NDA. The firm requested a telecon to obtain clarification of the deficiencies cited in the approvable letter. Those deficiencies from the action letter are listed immediately below.

Clinical/Biopharmaceutical:

1. After correcting for baseline values, the intranasal spray was 10% less bioavailable than the intranasal gel. This product is also less bioavailable than the intramuscular formulation. Since this product cannot be considered bioequivalent to the reference listed product, clinical use of this product or any cyanocobalamin formulation will require close monitoring of vitamin B_{12} levels. Patients not achieving adequate vitamin B_{12} levels will require increased dosing with subsequent blood monitoring.

    - Revise your package insert (PI) to include a discussion of the difference in pharmacokinetics of the two intranasal products and advice that patients treated with the nasal spray should have vitamin B_{12} levels closely monitored with dose amount and/or frequency adjusted to achieve adequate levels.

- Submit the revised draft labeling in your complete response. To facilitate our review, provide highlighted or marked up labeling. We are deferring additional comments on the PI labeling until we have received your response.

2. Change "room temperature" to "controlled room temperature" on the carton and container labels.

Regulatory Issues:

1. Submit Form FDA 3542a entitled "Patent Information Submitted With the Filing of an NDA, Amendment, or Supplement."

2. Clarify whether you are a full or partial assignee for patent #4,724,231.

MEETING OBJECTIVES:

The sponsor requested additional information about FDA's re-analysis of the bioequivalence data in order to provide the requested labeling revisions.

DISCUSSION POINTS:

Questions from the Sponsor for the Biopharmaceutics/Clinical reviewer *are shown in Italics;* responses from the FDA, **in Bold:**

Sponsor: What is the basis for the statement that the spray is 10% less bioavailable than the gel? If this is based on an FDA conducted re-analysis of the bioequivalence data, what is the FDA-determined relative bioavailability of gel vs IM, spray vs IM, and gel vs spray? In the ITT analysis submitted with NDA, the spray had an AUC of 104% relative to the gel with 95% CI of 97.7 – 111.2%. (NDA Volume 1.11, page 43). A total of three analyses were submitted with the NDA, and none of them came to the conclusion that the spray was 10% less bioavailable than the gel.

FDA: Baseline corrected analysis was done during the review process. The baseline value was obtained by taking the average of three pre-dose vitamin B12 concentrations in plasma. The relative bioavailability of gel vs. IM, spray vs. IM, and spray vs. gel was found to be 7.1%, 6.1%, and 90.4% respectively. The log transformed 90% confidence intervals for AUC(0-t) and Cmax were 71.71-114.19 and 71.6-118.66 respectively. The spray had 10% less bioavailability as compared to the gel; bioequivalency was not established.

Sponsor: What is meant by "after correcting for baseline values... "? Is this "baseline" the subject's endogenous B12 level, or is this in reference to the differences in potency between the tested gel and spray? If the difference in potency between the gel and spray was not accounted for in an FDA conducted re-analysis, we would like to discuss the "10% less bioavailable" conclusion, as the tested spray was — less potent than the gel. Note that in the submitted analysis where this — difference in potency was not corrected, the calculated bioavailability for spray/gel was 98%. (NDA Volume 1.12 page 281) If the "correction for baseline values" refers to subject's endogenous B12 levels, we would like to point out that we were advised by — which conducted the pharmacokinetic analysis, not to correct for baseline values, based on an FDA guidance for conducting bioequivalence studies.

This guidance, ***Guidance for IndustryLevothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing****, states*

> *"The plasma/serum profiles and pharmacokinetic measures should be presented without adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study."*

FDA Response: See response to previous question. The guidance for levothyroxine is specific for that only and is not applicable to other drugs.

Sponsor: What is the basis for the determination that "this product cannot be considered bioequivalent to the reference listed product"? What were the 95% confidence intervals in an FDA-conducted analysis? Were subjects or doses excluded from analysis? If so, on what bases were subjects or doses excluded?

FDA Response: See response to previous question.

DECISIONS (AGREEMENTS) REACHED:
The sponsor has agreed to include of discussion of the differences in bioavailability and a recommendation for careful monitoring.

The regulatory questions were not discussed in this meeting.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:
The Project Manager will contact the sponsor early next week regarding the regulatory questions.

ACTION ITEMS:
Internal meeting scheduled with CPMS Monday morning, T-con planned for November 23 or 24, 2004, depending on sponsor availability.

POST-MEETING NOTE:
On November 24, 2004, Ms. Galliers, Ms. Wieland, and Dr. Brandt consulted by telephone and addressed the regulatory questions. Dr. Brandt was advised that the correspondence submitted on March 24, 2004, constituted a complete response to the regulatory deficiencies, and that the deficiencies were fully corrected.

ATTACHMENTS/HANDOUTS:
None

Signed by: _____ Date: _____

Meeting Chair, _____ Date: _____

Recorded by: _____ Date: _____

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/s/

Holly Wieland
1/25/05 02:34:44 PM
CSO

Holly Wieland
1/25/05 02:39:49 PM
CSO

1/19/05

Memo to File

NDA #:	21-642
Sponsor:	Nastech Pharmaceutical Company, Inc.
Product:	Nascobal (vitamin B12) Nasal Spray
Medical Reviewer:	Mary H. Parks, MD Deputy Director Division of Metabolic and Endocrine Drug Products
Subject:	Response to AE letter

The applicant has submitted a response to an AE letter for NDA 21-642 dated October 28, 2004. This submission contains no clinical data; however, labeling review was required by the clinical team. The proposed changes made to the label by Dr. Jayabharathi Vaidyanathan from the Office of Clinical Pharmacology and Biopharmaceutics are acceptable. No additional changes are recommended by the clinical team.

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/s/

Mary Parks
1/19/05 01:19:06 PM
MEDICAL OFFICER

1/26/05

MEMORANDUM

Date:. January 19, 2005

To: NDA 21-642, N-000, Nascobal® Nasal Spray

From: Yvonne Yang, Ph.D.
Chemist Reviewer, HFD-510

Subject: Overall Compliance Recommendation

NDA 21-642 Nascobal® Nasal Spray was submitted Dec-20-2003. An Approvable letter dated Oct-28-2004 was issued by the Agency for (1) CMC (inspection at the drug substance manufacturing facility — has not been completed), and (2) Biopharm (Nascobal® Nasal Spray is not bioequivalent to the reference listed product). A complete response was submitted on Dec-01-2004.

An overall acceptable cGMP status has been granted by the Office of Compliance on Jan-12-2005 (see attached EER report for details).

All chemistry, manufacturing and controls sections of NDA 21-642 have been reviewed and found sufficient to support the approval of this application (see CMC review #1 dated Oct-07-2004 and this memo dated Jan-19-2005 for details).

From the standpoint of chemistry, manufacturing and controls, this NDA can be approved.

Cc: NDA # 21-642, N-000
HFD-510/Division file
HFD-510/Y Yang
HFD-510/M Gautam-Basak
HFD-510/H Wieland

12/02/04

MEMORANDUM

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

DATE: November 22, 2004

TO: Memo to File

FROM: Holly Wieland
Regulatory Project Manager

SUBJECT: NDA 21-642, Nascobal (cyanocobalamin) Nasal Spray
Clarification on Patent Questions
Addendum to February 24, 2004, Filing Review

In reference to the approvable letter dated, the review division identified two regulatory issues:

1) The sponsor should submit a form 3542a entitled, "Patent Information Submitted With the Filing of an NDA, Amendment, or Supplement."
2) The sponsor should clarify whether they are a full or partial assignee for patent #4,724,231.

The sponsor commented on November 12, 2004, that on March 24, 2004, they had submitted the Form 3542a and a notification of a licensing agreement and a consent to an immediate effective date by Questcor upon approval of NDA application 21-642. Enid Galliers, CPMS, and I verified the submissions.

Form 3542a does not claim any patents.

This March 24, 2004, submission included a letter dated March 19, 2004, from Questcor Pharmaceuticals Inc., with the original signature. The letter certified that Questcor is the patent holder of U.S. Patent No. 4.724,231, and has been notified by Nastech Pharmaceutical Company, Inc. that NDA application 21-642, which references U.S. Patent No. 4, 724,231 has been filed, that Nastech Pharmaceutical Company, Inc. has a licensing agreement with Questcor Pharmaceuticals Inc., and that the patent owner, Questcor Pharmaceuticals Inc. consents to an immediate effective date upon approval of NDA 21-642.

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/s/

Holly Wieland
12/2/04 09:48:05 AM
CSO

NASTECH
PHARMACEUTICAL COMPANY INC.

November 8, 2004

Holly Wieland, R.N., M.P.H.
Regulatory Project Manager
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products (HFD510)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Via e mail to: WielandH@cder.fda.gov

RE: NDA No. 21-642
Nascobal® (Cyanocobalamin, USP) Spray for Intranasal Administration
Request for clarification on patent question

Dear Ms. Wieland:

To follow up on the action letter of October 28, 2004, Nastech requests clarification of item 4, which is reproduced below. The issue for us is that we believe we have already answered this question in a prior submission, and we therefore don't know what additional information or clarification is required. If you would be so kind as to request clarification from ORA (or whomever originated this item), it would be very helpful.

Item 4 from the Action letter states:

4. Regulatory Issues:

- Submit Form FDA 3542a entitled "Patent Information Submitted With the Filing of an NDA, Amendment, or Supplement."
- Clarify whether you are a full or partial assignee for patent #4,724,231.

We previously submitted Form 3542a as NDA Amendment 4 on March 24, 2004. The relevant parts of that submission are attached below and included the following:

- Signed paragraph 4 certification
- Completed Form 3542a
- Statement from the owner of patent 4,724,231 (Questcor Pharmaceuticals) that Nastech has a license to that patent.

Corporate Headquarters: 3450 Monte Villa Parkway • Bothell, WA 98021 • Tel: (425) 908-3600 • Fax: (425) 908-3650
45 Davids Drive • Hauppauge, NY 11788 • Tel: (631) 273-0101 • Fax: (631) 273-2469
www.nastech.com

Patent 4,724,231 is identified in the Paragraph 4 certification, and applies only to the Gel formulation of nasal B12 (NDA 19-722). For the current NDA (the Spray formulation, NDA 21-642) which is filed as a 505(b)2 application referencing the prior NDA 19-722, we do not have any patents which are relevant to be placed in the Orange Book. Also please note that as described in the March 24, 2004 filing, Nastech is a licensee, and therefore is neither a full or partial assignee for patent 4,724,231.

Attachment 4 from the March 24, 2004 submission is included as confirmation of Questcor's licensing the patent to Nastech.

Thank you very much for your assistance in clarifying what additional information we can supply regarding this issue. We are hoping to submit a response to the action letter the week of November 15, so we urgently await this clarification.

Gordon Brandt

Gordon Brandt, M.D.
Executive Vice President
Clinical Research & Medical Affairs

Lab Review
10/28/04

Division of Metabolic and Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-642

Name of Drug: Nascobal (cyanocobalamin) Nasal Spray

Applicant: Nastech Pharmaceutical Company Inc.

Material Reviewed:

Submission Date:	September 17, 2004	**Receipt Date:** September 20, 2004
Package Insert:	Product Identifier #3065	Rev. Date 09/04
Container Label:	Product Identifier #3064;	Rev. Date 09/04
Submission Date:	October 13, 2004	**Receipt Date:** October 13, 2004
Carton Label:	Product Identifier #2062	Rev. Date 09/04

Background and Summary

The sponsor has proposed to submit this application, NDA 21-642, as a 505 (b)(1) application with full right of reference to NDA 19-722, Nascobal (cyanocobalamin) Gel, approved November 5, 1996. However, NDA 19-722 has been reassessed as a 505(b)(2) NDA because it did not provide full clinical and preclinical studies. This application for Nascobal Nasal Spray relies on a bioequivalence study that compared the nasal spray to the nasal gel.

The active ingredient, cyanocobalamin, and the strength of the active ingredient per dose, 500 mcg/0.1 mL, were identical. The difference between the two products is the dosage form.

The **proposed labeling for the package insert** for (Product Identifier #3065, Revision Date 9/04) was compared to the final printed label (FPL) for the package insert for Nascobal Gel (Product Identifier #3058, Revision Date 10/03 (S-006 approved August 21, 2003).

The **proposed container label** for Nascobal Nasal Spray (Product Identifier #3064, Revision Date September 2004) was compared to the FPL for the container label for Nascobal Gel (Product Identifier #3051, Revision Date June 2003).

The **proposed carton label** for Nascobal Nasal Spray (Product Identifier #2062 Revision Date September 2004) was submitted on October 13, 2004. FDA never received FPL for any Nascobal Gel carton.

The **Patient Instructions** have been included in the PI as item #2 in the PRECAUTIONS Section, at the end of the PI, and on the back panel of the carton label.

Review

Package Insert (PI):

1. In the **DESCRIPTION** section, third paragraph beginning, "NASCOBAL® (Cyanocobalamin, USP) . . ." there is wording reflecting the product name change and description from "NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration is a solution of Cyanocobalamin, USP (vitamin B_{12}) for administration as a metered gel to the nasal mucosa" to "Nascobal® Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B_{12}) for the administration of a spray to the nasal mucosa."

2. In the third paragraph, all references to "gel" or "metered gel" have been changed to "spray" or "metered spray."

3. In the third paragraph, in the list of ingredients beginning with the words, "Each bottle of Nascobal®. . ." methylcellulose has been deleted.

4. In the third paragraph, there is a change in the priming instructions, from, "The gel pump unit must be fully primed (see Patient Instructions) prior to initial use. After initial priming, each metered gel delivers an average of 500 mcg of cyanocobalamin and the 2.3 mL of gel contained in the bottle will deliver 8 doses of Nascobal®. If the unit is kept upright, repriming between doses should not be necessary (see Patient Instructions)" to "The spray pump unit must be fully primed (see Dosage and Administration) prior to initial use. After initial priming, each spray delivers an average of 500 mcg of cyanocobalamin and the 2.3 mL of spray solution contained in the bottle will deliver 8 doses of Nascobal Nasal Spray. The unit must be re-primed before each dose. (see Dosage and Administration)."

5. In the **PHARMACOKINETICS** section, data from the bioequivalence study has been added after the second paragraph ending, "100mcg intramuscular dose (Figure). The wording is as follows:

6. In the **INDICATIONS AND USAGE** section, the wording in the first paragraph has been changed to reflect the product name change and reads, "Nascobal® Nasal Spray is indicated for the maintenance of normal hematologic status in pernicious anemia patients

who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement."

7. In the **INDICATIONS AND USAGE** section, the wording in the second paragraph has been changed to reflect the product name change and reads, "Nascobal® Nasal Spray is also indicated as a supplement for other vitamin B_{12} deficiencies, including: . . ."

8. In the **INDICATIONS AND USAGE** section, the wording in the last paragraph has been changed to reflect the product name change and reads, "Nascobal® Nasal Spray is not suitable for vitamin B_{12} absorption test (Schilling Test)."

9. The **WARNINGS** section has been revised to include reference to the nasal spray and reads, 'No such reactions have been reported in clinical trials with Nascobal® Nasal Spray or Nascobal® Nasal Gel."

10. The **PRECAUTIONS (1.GENERAL)** section has been revised to reflect the product name change from "Nascobal® (Cyanocobalamin, USP) Gel for Intranasal Administration" to "Nascobal® Nasal Spray. This product name change is seen in paragraphs 1, 7, and 8.

11. The **PRECAUTIONS (2.INFORMATION FOR PATIENTS)** section has been revised to reflect the product name change from "Nascobal® (Cyanocobalamin, USP) Gel for Intranasal Administration" to "Nascobal® Nasal Spray. This product name change is seen in paragraphs 1, 2, 3, and 5.

12. The **PRECAUTIONS (3. LABORATORY TESTS)** section has been revised to reflect the product name change from "Nascobal® (Cyanocobalamin, USP) Gel for Intranasal Administration" to "Nascobal® Nasal Spray. This product name change is seen in paragraphs 1 and 2.

13. In the **PRECAUTIONS (3. LABORATORY TESTS)** section, paragraph 3 has a word change from "nasal gel" to "nasal spray."

14. The **ADVERSE REACTIONS** section has a second paragraph added to reference the bioequivalence study which states, "In the pharmacokinetic study comparing Nascobal Nasal Spray and Nascobal Nasal Gel, the incidence of adverse events was similar."

15. The **OVERDOSAGE** section has been revised from, "No overdosage has been reported with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration or parenteral vitamin B_{12}" to "No overdosage has been reported with Nascobal Nasal Spray, NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration, or parenteral vitamin B_{12}.

16. The **DOSAGE AND ADMINISTRATION** section has been revised from, "The

recommended initial dose of NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration in patients with vitamin B_{12} malabsorption who are in remission following injectable vitamin B_{12} therapy is 500 mcg administered intranasally once weekly. Patients should be in hematologic remission before treatment with NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration" to "The recommended initial dose of Nascobal Nasal Spray is one spray (500 mcg) administered in ONE nostril once weekly. Nascobal Nasal Spray should be administered at least one hour before or one hour after ingestion of hot foods or liquids.

17. There is an additional paragraph in the **DOSAGE AND ADMINISTRATION** section entitled, "Priming (Activation) of the Pump." The new paragraph reads as follows, "Before the first dose and administration, the pump must be primed. To prime the pump, place nozzle between the first and second finger with the thumb on the bottom of the bottle. Pump the unit firmly and quickly until the first appearance of spray. Then prime the pump an additional 2 times. Now the nasal spray is ready for use. The unit must be re-primed before each dose. Prime the pump once immediately before each administration of doses 2 through 8."

18. Attached to this labeling review is a set of pictorials demonstrating how to prime the pump.

19. The **HOW SUPPLIED** section has been revised to reflect the product name change from "Nascobal® (Cyanocobalamin, USP) Gel for Intranasal Administration" to "Nascobal® Nasal Spray. In the first sentence, the words, "a metered dose gel in 5 mL glass bottles containing 2.3 mL gel" have been changed to "a spray in 3 mL glass bottles containing 2.3 mL solution."

20. In this same paragraph, the words, "gel" or "metered dose gel" have been changed to "spray" or "nasal spray solution."

21. There is a new NDC number for this product, NDC 63004-7733-5.

22. The **PHARMACIST ASSEMBLY . . .** section has been revised to reflect the product name change from "**NASCOBAL® (CYANOCOBALAMIN, USP) GEL FOR INTRANASAL ADMINISTRATION" TO "NASCOBAL® NASAL SPRAY.**"

23. This change is also seen in the first paragraph, and in Steps 2 and 3, from "NASCOBAL® (cyanocobalamin, USP) Gel for Intranasal Administration" to "Nascobal® Nasal Spray."

24. In the **PHARMACIST ASSEMBLY . . .** section, in Steps 1-3, the words "gel" or "gel solution" have been changed to "spray" or "spray solution."

25. In the **PHARMACIST ASSEMBLY . . .** section, following Step 2, a set of pictorials have been included to demonstrate assembly instructions.

26. There is an additional section after the **PHARMACIST ASSEMBLY . . .** section entitled, "**INFORMATION FOR PATIENTS.**" This is an exact reprint of **2. INFORMATION FOR PATIENTS** included in the **PRECAUTIONS** section on a previous page. It is included at the bottom of the package insert as required by 21CFR201.57(f)(2).

    INFORMATION FOR PATIENTS "Patients with pernicious anemia should be instructed that they will require weekly intranasal administration of Nascobal Nasal Spray for the remainder of their lives. Failure to do so will result in return of the anemia and in development of incapacitating and irreversible damage to the nerves of the spinal cord. Also, patients should be warned about the danger of taking folic acid in place of vitamin B_{12}, because the former may prevent anemia but allow progression of subacute combined degeneration of the spinal cord.

    (Hot foods may cause nasal secretions and a resulting loss of medication; therefore, patients should be told to administer Nascobal Nasal Spray at least one hour before or one hour after ingestion of hot foods or liquids).

    A vegetarian diet which contains no animal products (including milk products or eggs) does not supply any vitamin B_{12}. Therefore, patients following such a diet should be advised to take Nascobal Nasal Spray weekly. The need for vitamin B_{12} is increased by pregnancy and lactation. Deficiency has been recognized in infants of vegetarian mothers who were breast fed, even though the mothers had no symptoms of deficiency at the time.

    The patient should also understand the importance of returning for follow-up blood tests every 3 to 6 months to confirm adequacy of the therapy.

    Careful instructions on the actuator assembly, priming of the actuator and nasal administration of Nascobal Nasal Spray should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient."

27. In the **STORAGE CONDITIONS** section, the word, "controlled" has been deleted.

28. There is an updated Product Identifier Number: 3065 and Revision Date: 9/04

    - The Pharmacology Reviewer found the PI labeling acceptable.

    - The Chemist found the PI labeling acceptable. The deletion of methylcellulose in item #3 is acceptable because it is necessary in the gel formulation, not the spray formulation.
    - The Biopharmaceutical Reviewer did not comment on labeling because the spray and gel did not demonstrate bioequivalence. However, the Medical Reviewer

recommended revision of the PI to discuss the difference in pharmacokinetics and to add advice that patients treated with the nasal spray should have vitamin B_{12} levels closely monitored with dose amount and/or frequency adjusted to achieve adequate levels.

Container Label:

1. There is a product name change from, "nascobal® (Cyanocobalamin, USP) Gel for Intranasal Administration" to "nascobal® Nasal Spray"

2. The strength description has been modified slightly from "500 mcg/mL" to "500 mcg/spray" and the words, "(8 sprays) have been added after 2.3 mL.

3. The NDC number has been revised to "NDC 63004-7733-5."

4. The storage instructions have been revised to read, "STORE UPRIGHT AT ROOM TEMPERATURE 15°-30°C (59°- 86°F)." The word, "Controlled" was deleted.

5. The statement, "Each 1.0 mL . . ." on the gel container label was deleted from the spray container label.

6. The statement, "SEE PACKAGE INSERT. . ." on the gel container label was deleted from the spray container label.

7. The statement, "SEE ENCLOSED DIRECTIONS . . ." on the gel container label was deleted from the spray container label.

8. The words, "For use in ONE nostril unless otherwise directed by your physician" have been added to the spray container label.

9. The new product identifier number is 3064. The new revision date is Rev. 9/04.

    - The Chemist recommended adding the word "controlled" back to item #4 to say, "controlled room temperature."

Carton Label:

Changes on the front panel (FP) include:

1. the product name change from, "NASCOBAL® (Cyanocobalamin, USP) Gel for Intranasal Administration" to "nascobal® nasal spray"

2. the strength description change from "500 mcg/mL" to "500 mcg/spray" and the words, "(8 sprays) have been added after 2.3 mL

3. the addition of the words "FOR NASAL USE ONLY"

4. the deletion of methylcellulose from the list of ingredients

5. the addition of the statement, "Read instructions carefully before using."

6. the storage instructions change, from "store upright at controlled room temperature 15°-30°C (59°- 86°F)" to, "store upright at room temperature 15°-30°C (59°- 86°F)."

7. the words, "Protect from light" and "Protect from freezing" were added under the statement, "Store upright at room . . ."

8. the addition of Rx Only

9. the Questcor Logo has a registered mark, "®" and is followed by "Manufactured for Questcor Pharmaceuticals, Inc. Union City, CA 94587 USA." Nastech is not mentioned on the label.

10. the revised NDC number from "NDC 63004-7732-4" to "NDC 63004-7732-5"

11. the revised product identifier, 2062 and revision date, 9/04

Changes on the back panel (BP) include:

1. Step 2, the product name changed from, "NASCOBAL® " to "nascobal® nasal spray"

2. Step 2, "pump gel unit. . ." changed to "pump unit FIRMLY AND QUICKLY until first appearance of spray."

3. Step 3, the addition of "(½")"

4. Step 5, delete reference to "gel"

5. Step 6, delete wording, "Massage to dosed nostril gently a few seconds. (Fig. 3)"

6. Step 7, different priming instructions from, "If kept upright, repriming between doses should not be necessary. Otherwise repriming may reduce the amount of medicine available" to "Reprime **once** before each dose."

7. Step 7, a word change, from, ". . . upright in container" to " . . .upright in carton"

8. adding discard instructions in Step 8, "Discard the bottle . . ." and moving the statement, "The best way . . ." from side panel 2 (SP2) to the end of Step 8

Changes to side panel 1 (SP1) include:

1. revised wording from, "USUAL DOSE: ONE Dose. Dose ONLY ONCE into ONLY ONE nostril. DO NOT dose into both nostrils unless directed by your doctor. DO NOT repeat sooner than directed by your doctor" to "USUAL DOSE: Usual dosage one spray (500 mcg) into only ONE nostril once weekly. Do not dose into both nostrils unless directed by your doctor. Do not repeat sooner than directed by your doctor. Discard the bottle after the 8th dose."

2. deletion of paragraph, "NOTE: THE VIAL IS PREFILLED . . ."

Changes to side panel 2 (SP2) include:

1. relocation of the disposal statement, "The best way to safely dispose . . ." to the BP at the end of Step 8.

2. a change in typeface for the product name from "NASCOBAL®" to "Nascobal® Nasal Spray"

    - The Chemist found the container labeling acceptable with one revision, to change from "room temperature" to "controlled room temperature."

Conclusions: Items Reviewed

Package Insert (Submitted September 17, 2004): Product Identifier #3065 Rev. Date 09/04
Container Label (Submitted September 17, 2004): Product Identifier #3064 Rev. Date 09/04
Carton Label (Submitted October 13, 2004) Product Identifier #2062 Rev. Date 09/04

We are conveying the container and carton deficiencies in an AE letter. The Chemistry reviewer has recommended adding the word "controlled" the storage information so that it reads, "controlled room temperature" on the PI, container, and carton. We are deferring comment on the PI until the sponsor addresses the bio-inequivalence issue in the PI.

Holly Wieland, RN, MPH
Regulatory Project Manager
DMEDP, HFD-510
CDER

Supervisory Comment/Concurrence:

Enid Galliers
Chief, Project Management Staff

Drafted: HWieland/09/28/04
Revised/Initialed:10/21/04;10/27.04
Filename: RPM labeling review.doc

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/s/

Holly Wieland
10/28/04 09:08:17 AM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-642	Efficacy Supplement Type SE-	Supplement Number	
Drug: Nascobal (Cyanocobalamin, USP) Spray for Intranasal Administration		Applicant: Nastech Pharmaceutical Company, Inc.	
RPM: Holly Wieland, RN, MPH		HFD-510	Phone # 301-827-6410
Application Type: ( ) 505(b)(1) **(X)** 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 19-722 Nascobal Intranasal Gel	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 29, 2004
❖ 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	**(X)** Paid UF# 4528
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ 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)	
• OC clearance for approval	
❖ 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.	(*) *Requested in AE letter
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III **(X)** IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	**(X)** **Applicant claims to be assignee.**

❖ Exclusivity (approvals only)	
• Exclusivity summary	10/25/04
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	02/24/04, 03/09/04
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA **(X)** AE ( ) NA
• Previous actions (specify type and date for each action taken)	None
• 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	( ) 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)	NA
• Most recent applicant-proposed labeling	10/18/04
• Original applicant-proposed labeling	12/26/03
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	08/04/04 DMETS Consult Complete 09/28/04 Draft Labeling Review 10/28/04 AE Lab. Review
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	09/16/04 Labeling amendment
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	10/18/04
• Reviews	09/28/04 Draft Labeling Review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**Included**
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	12/05/01

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	NA
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	10/19/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	NA
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	10/21/04
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	NA
❖ Biopharmaceutical review(s) *(indicate date for each review)*	10/01/04 BP Review 10/06/04 BP Addendum
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	03/10/03 DSI Consult Sent 06/30/04 DSI Response 09/17/04 DSI Addendum
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	02/25/04 Acceptable for filing 08/20/04 DMF Review 10/08/04 Review-AE recommended
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	10/08/04
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	10/08/04
❖ Facilities inspection (provide EER report)	Date completed: 10/29/04 ( ) Acceptable **(X)** Withhold recommendation* *One site not ready for inspection
❖ Methods validation	**(X)** Completed ( ) Requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	02/09/04 Acceptable for filing 06/28/04 Approval recommended
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

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/s/

Holly Wieland
10/27/04 09:20:32 AM

DFS 10/21/04

AMENDED NDA REGULATORY FILING REVIEW
(Update of 02/24/04 Filing Review)

NDA #	21-642
Trade Name:	Nascobal Nasal Spray
Generic Name:	cyanocobalamin
Strengths:	500mcg/0.1 mL
Applicant:	Nastech Pharmaceutical Company Inc.
Date of Application:	December 26, 2003
Date of Receipt:	December 29, 2003
User Fee Goal Date:	October 29, 2004

Indication(s) requested: Maintenance of normal hematologic status in pernicious anemia patients.

Type of Original NDA: (b)(1) _____ (b)(2) **XX**

APPEARS THIS WAY
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Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES **XX**

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

   NDA 19-722 Nascobal Intranasal Gel

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

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

   NO **XX**

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

4. (a) Is there a pharmaceutical alternative(s) already approved? YES **XX**

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

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES **XX**
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   *If "**No**," skip to question 6.*

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

   This application provides for a change in dosage form from an intranasal gel to an intranasal spray.

6.	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 (see 21 CFR 314.101(d)(9)).	NO	**XX**
7.	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 21 CFR 314.101(d)(9)).	NO	**XX**
8.	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 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9).	NO	**XX**
9.	Are there certifications for each of the patents listed for the listed drug(s)?	YES	**XX**

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

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

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

    ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

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

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

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

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

____ 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.

11. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES **XX**

This application relies on the prior approval of NDA 19-722.

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

NO **XX**

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

YES **XX**

- 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).?

NO **XX**

12. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

Not Applicable

13. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application

YES **XX**

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/s/

Holly Wieland
10/21/04 02:26:12 PM
CSO

Holly Wieland
10/21/04 02:31:14 PM
CSO

PW 10-14-04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-642
Nastech Pharmaceutical Company, Inc.
Attention: Gordon Brandt, M.D.
Executive Vice President, Clinical Research and Medical Affairs
45 Davids Drive
Hauppauge, NY 11788

Dear Dr. Brandt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nascobal® (cyanocobalamin) Nasal Spray.

We also refer to your letter dated March 22, 2004, requesting a waiver of the requirement to conduct pediatric studies.

We have reviewed the referenced material and determined that pediatric studies are not needed. Your request for a waiver is granted.

If you have any questions, call Holly Wieland, Regulatory Project Manager, at 301-827-6410.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kati Johnson
10/14/04 05:41:42 AM
signing for David Orloff, MD

Wieland, Holly

From: ees_admin@bambi.cder.fda.gov
nt: Wednesday, September 29, 2004 4:00 PM
: WIELANDH@cder.fda.gov
ubject: Firm Not Ready DO-INT NDA 21642/000 CFN: [redacted] rofile:CFS

This is a system generated email message to notify you that there is a District Recommendation with Reason 'Firm Not Ready' for the above EER.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@CDER.FDA.GOV).
To contact the EES technical staff, send an email to CDER EES Help (EESHELP@CDER.FDA.GOV). Thank you.

A

2 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

NASTECH
PHARMACEUTICAL COMPANY INC.

ORIGINAL

N 000 BB
ORIG AMENDMENT

August 31, 2004

Holly Wieland, R.N., M.P.H.
Regulatory Project Manager
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products (HFD510)
Food and Drug Administration
5600 Fishers Lane
Att: Fishers Document Room, 8B45
Rockville, MD 20857

RECEIVED
SEP 0 1 2004
FDA/CDER

VIA FEDERAL EXPRESS

Re: NDA No. 21-642
Nascobal® (Cyanocobalamin) Nasal Spray

Dear Ms. Wieland:

To follow up on our conversation of today, please find attached a copy of the — 483 response which was sent to the Baltimore District office on 30jul04. This response contains data indicating that cyanocobalamin clinical samples are stable at -20degC for at least 28 days, which is longer than the time between sample acquisition and analysis for the bioequivalence study submitted with NDA 21-642. I understand that Dr. Vishwanadhan was waiting for this response before completing his review.

Would you please pass this document along to Dr. Vishwanadhan so that he can complete his review?

Thank you very much for your assistance in the review of NDA 21-642. Please contact me at (425) 908-3640 if you should require additional information. Fax communications can be directed to (425) 908-3655.

Sincerely,

Gordon Brandt, M.D.
Executive Vice President
Clinical Research & Medical Affairs
Nastech Pharmaceutical Company, Inc.

RECEIVED
CDER/FDA/OSI
HFD-45
2004 SEP -9 PM 2:48

Corporate Headquarters: 3450 Monte Villa Parkway • Bothell, WA 98021 • Tel: (425) 908-3600 • Fax: (425) 908-3650
45 Davids Drive • Hauppauge, NY 11788 • Tel: (631) 273-0101 • Fax: (631) 273-2469
www.nastech.com

NDA 21-642

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: May 5, 2004	**DESIRED COMPLETION DATE:** July 5, 2004 **PDUFA DATE:** October 29, 2004	**ODS CONSULT #:** 04-0151

TO: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Holly Wieland
Project Manager
HFD-510

PRODUCT NAME:	**SPONSOR:** Nastech Pharmaceutical Company, Inc.
Nascobal® Nasal Spray (Cyanocobalamin, USP) 500 micrograms/0.1 mL **NDA #: 21-642**	

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Nascobal® Nasal Spray. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Nascobal® Nasal Spray acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PRE-MARKETING LABELING REVIEW

DATE OF REVIEW: June 25, 2004

NDA: 21-642

NAME OF DRUG: **Nascobal® Nasal Spray**
(Cyanocobalamin, USP)
500 micrograms/0.1 mL

NDA SPONSOR: Nastech Pharmaceutical Company, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products, for an assessment of the proprietary name "Nascobal® Nasal Spray" regarding potential name confusion with other proprietary or established drug names. Nascobal® Nasal Spray is a new formulation of an already approved drug product, Nascobal® Intranasal Gel. The gel was approved by the Agency on November 15, 1996 (NDA 19-722). This nasal spray formulation is the first product line extension of the gel. The products are identical in indication, strength, and dosing regimen. They differ only in dosage form. Draft container labels, carton package insert labeling were provided for review and comments.

PRODUCT INFORMATION

Nascobal® Nasal Spray contains the active ingredient cyanocobalamin. It is indicated for the maintenance of normal hematologic status in pernicious anemia patients who are in remission following intramuscular vitamin B_{12} therapy and who have no nervous system involvement. It is also indicated as a supplement for other vitamin B_{12} deficiencies, including pernicious anemia, dietary vitamin B_{12} deficiency, and malabsorption of vitamin B_{12} resulting from structural of function damage to the stomach. The recommended initial dose of Nascobal® Nasal Spray is one spray (500 micrograms) administered intranasally once weekly.

II. RISK ASSESSMENT:

DMETS did not perform the standard trade name review for the proposed name, Nascobal® Nasal Spray since the root name, Nascobal®, has been utilized in the U.S. Marketplace since November, 1996. The FDA Adverse Event Reporting System (AERS), and the Drug Quality Reporting System (DQRS) were searched to determine if there is any confusion reported with the use of the proprietary name Nascobal®.

A. AERS AND DQRS DATABASE SEARCH

In order to determine the degree of name confusion with Nascobal and other approved drug products already on the U.S. market, DMETS searched the F*DA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Nascobal®. The MedDRA Preferred Term (PT), "Medication Error" and the drug name "Nascobal%", and "cyanocobalamin", were used to perform these searches. In addition, the Drug Quality Reporting System *(DQRS)* database was searched for similar reports. These search strategies did not yield any medication errors reports involving Nascobal.

B. SAETY EVALUATOR RISK ASSESSMENT

To date, the Agency has not received any medication error reports involving name confusion or dosing errors with Nascobal. However, with the introduction of the spray there is potential for confusion among the Nascobal product line.

Nascobal Nasal Spray contains the same active ingredient (cyanocobalamin), and at the same concentration and strength (500 micrograms per 0.1 mL), as the currently approved Nascobal Intranasal Gel. Although the products differ in dosage form (spray vs. gel), both are administered intranasally once a week. Because these products are identical in active ingredient and strength, if a prescription where written for Nascobal Intranasal Gel, and the nasal spray were dispensed, or vice versa, patients would not experience harm to be exposed to increased side effects of the medication. However, it would be beneficial to educate healthcare professionals on this new formulation. Additionally, the labels and labeling should be differentiated to help minimize selection errors between these formulations.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the draft container label, carton and package insert labeling for Nascobal Nasal Spray, DMETS has focused on safety issues relating to possible medication errors, and has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. Please relocate the net quantity statement so that it does not appear in conjunction with the product strength. In addition a statement should be placed in conjunction with the mL amount that indicates the number of sprays available in each bottle. For example 2.3 mL (approximately 8 doses).

2. Please revise the strength to read "500 mcg/spray" rather than "500 mcg/0.1 mL" since the dose is based on the number of sprays rather than a "mL' amount.

3. This product is unique in that it is administered via one nostril. Most nasal sprays are administered via both nostrils. Thus, we can anticipate user error with this dosage form. A statement should be prominently placed on the principal display panel "For use in ONE nostril, unless otherwise directed by your physician".

B. CARTON LABELING

1. See comment under A-1 and A-2 under CONTAINER LABEL.

2. Please revise the usual dosage statement to read "Usual dosage: one spray (500 micrograms) into only one nostril once weekly. Do not dose into both nostrils unless directed by your doctor. Do not repeat sooner than directed by your doctor. Discard the bottle after the eighth dose".

3. Please relocate the statement "The best way to safely dispose of the unit....." from the side panel to the end of the Patient Instructions section. In addition, precede this statement with "Discard the bottle after the eighth dose".

4. Please include the "Rx only" statement.

C. PACKAGE INSERT LABELING

1. In the "Pharmacists Assembly Instruction", please include pictorials which outline the steps for assembly.

2. The Information for Patients subsection provides important information that needs to be conveyed to the patient. Thus, this information must be reprinted at the end of the insert, per 21 CFR 201.57(f)(2).

4. Dosage and Administration Section

   a. The dosage and administration section does not make reference to the fact that this product is delivered via only one nostril. It also does not convey the important information such as not administering at least one hour before or after ingestion of hot foods or liquids. We recommend revising this section as follows: "The recommended initial dose of Nascobal nasal Spray is one spray (500 mcg) administered in ONE nostril once weekly. Nascobal Nasal Spray should be administered at least one hour before or one hour after ingestion of hot foods or liquids".

   b. Priming (Activation) of Pump subsection

      Please include pictorials with the description of the priming (activation) of the pump.

III. RECOMMENDATIONS

A. DMETS has no objections to the use of the proprietary name, Nascobal Nasal Spray. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Tia Harper-Velazquez
8/4/04 10:00:30 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/4/04 10:45:57 AM
DRUG SAFETY OFFICE REVIEWER

B

21 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Nastech Pharmaceutical Co. Inc.	3/24/04
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
631-273-0101	631-273-2469
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
45 Davids Drive Hauppauge, NY 11788	N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-642

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Cyanocobalamin Nasal Spray	Nascobal

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
5, 6-dimethyl-benzimidazolyl cyanocobamide	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Nasal Spray	500 mcg/0.1 mL	Intranasal

(PROPOSED) INDICATION(S) FOR USE:

intenance of normal hematologic status in pernicious anemia patients and supplementation for other vitamin B12 deficiencies

LICATION DESCRIPTION

LICATION 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
Response to FDA questions in filing communication letter of March 1, 2004

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

NUMBER OF VOLUMES SUBMITTED N/A 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.

N/A

s 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)* Response to FDA questions in filing communication letter of March 1, 2004

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:
Gordon Brandt MD	Gordon Brandt, Executive VP of Clin & Med Affairs	3/24/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3450 Monte Villa Pkwy., Bothell, WA 98021	(425) 908-3640

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:

epartment of Health and Human Services
d and Drug Administration
ER, HFD-99
01 Rockville Pike
Rockville, 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.

NASTECH
PHARMACEUTICAL COMPANY INC.

Corporate Headquarters
3450 Monte Villa Parkway
Bothell, WA 98021
Tel: (425) 908-3600
Fax: (425) 908-3650
www.nastech.com

45 Davids Drive
Hauppauge, NY 11788
Tel: (631) 273-0101
Fax: (631) 273-2469

420 Lexington Avenue
Suite 300
New York, NY 10170
Tel: (212) 297-6191
Fax: (212) 479-2554

March 24, 2004

Holly Wieland, R.N., M.P.H.
Regulatory Project Manager
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products (HFD510)
Food and Drug Administration
5600 Fishers Lane
Att: Fishers Document Room, 8B45
Rockville, MD 20857

VIA FEDERAL EXPRESS

Re: NDA No. 21-642
Nascobal® (Cyanocobalamin) Nasal Spray
Response to Filing Communication

Dear Ms. Wieland:

This serves as a complete response to FDA's filing communication letter dated March 1, 2004 for the above referenced new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

With regard to item 5, FDA's request for a nasal spray actuator and filled vial, per Nastech SOP, we request acknowledgement for receipt of this sample. Please open the enclosed box, fill in the "Quantity Received" on the Inventory Transfer Form, sign and date the form, and return to Nastech in the envelope provided.

Please contact me at (425) 908-3640 if you should require additional information. Fax communications can be directed to (425) 908-3655.

Sincerely,

Gordon Brandt MD

Gordon Brandt, M.D.
Executive Vice President
Clinical Research & Medical Affairs
Nastech Pharmaceutical Company, Inc.

3/9/04

MEMORANDUM

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

DATE: February 27, 2004

TO: Files: NDA 21-642 and NDA 19-722

THROUGH: Enid Galliers, Chief, Project Management Staff, DMEDP
Consult: Lee Ripper, Associate Director for Regulatory Affairs, Office of Drug Evaluation II

FROM: Holly Wieland, Regulatory Project Manager, DMEDP

SUBJECT: Determination of 505(b)(2) classification of NDA 21-642 Nascobal Nasal Spray and Listed Drug NDA 19-722 Nascobal Gel

We believe that NDA 21-642 Nascobal (cyanocobalamin) Nasal Spray was submitted pursuant to section 505(b)(2) despite having full right of reference to NDA 19-722 Nascobal (cyanocobalamin) Gel that was approved November 5, 1996. The rationale for this change is as follows.

The form 356h for Nascobal Gel application (NDA 19-722) identified the NDA as a 505(b)(1) application. At the time NDA 19-722 was submitted, an applicant's classification of a drug product as a (b)(1) or (b)(2) was usually not reviewed or questioned. The Nascobal Gel application (NDA 19-722) consisted of pharm/tox data from three rabbit nasal mucosal irritation studies, one rat pharmacokinetic (PK) study, one human bioavailability study (25 patients with pernicious anemia received one month (one dose) of intramuscular dosing with 100 mg B12 followed by one month (four doses) of intranasal dosing with 500 mg B12), and an extensive bibliography to support clinical efficacy and safety claims.

Because the Nascobal Gel (NDA 19-722) application does not contain any clinical safety and efficacy data or the usual battery of preclinical trials, and relies on literature for safety and efficacy claims, it does not qualify as a 505(b)(1) as originally classified by the applicant and should have been considered to be a 505(b)(2) application. Therefore, we consider NDA 21-642 to have been submitted pursuant to section 505(b)(2).

The NDA Filing Review and Minutes for NDA 21-642 (dated February 24, 2004) Nascobal Nasal Spray should be amended to reflect these changes.

1. Page 1, change the determination of 505(b) classification from 505(b)(1) to "505(b)(2)".
2. Page 4, add the name of the listed drug and NDA, "NDA 19-722 Nascobal Gel".
3. Page 4, add the change in dosage form to "This application provides for a change in dosage form from a gel to a nasal spray".

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

/s/

Holly Wieland
3/9/04 10:11:56 AM
CSO

Enid Galliers
3/9/04 10:32:18 AM
CSO

Leah Ripper
3/9/04 12:02:34 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-642

3-2-04

Nastech Pharmaceutical Company, Inc.
Attention: Gordon Brandt, MD
Executive Vice President of Science and Clinical Development
45 Davids Drive
Hauppauge, NY 11788

Dear Dr. Brandt:

Please refer to your December 26, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nascobal (cyanocobalamin nasal spray) 500 mcg/0.1 mL.

We also refer to your submission dated January 15, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 27, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. The footnotes for Table P.5.1-1 (page 249) and Table P.5.2-1 (page 250) indicate inconsistency in spray performance characterization testing. The testing for pump delivery, spray pattern, and droplet size distribution should be performed for routine release testing of the drug product. The proposed regulatory drug product specifications should be revised to include pump delivery, spray pattern, and droplet size distribution.

2. The Letters of Authorization (LOA) for DMF — and DMF — incomplete. Please provide volume and page number for the specific item referenced in the DMF. Revised LOAs with the requested information should be submitted.

3. Provide representative HPLC chromatograms for Assay/Impurities and Degradation Products, at — time points, for stability testing at the accelerated condition (40°C/75% RH).

4. Provide detailed container/closure component information for container/closures used in the stability studies listed in Table P.8.3-1 (Volume 1.4, page 387).

5. Provide a sample of the nasal spray pump and the drug product for reference.

6. Submit a signed copy of the Paragraph IV patent certification.

7. Submit Form FDA 3542a (7/03).

8. Submit a signed certification that the patent holder has been notified that the application has been filed and documentation that the patent holder received the notification.

9. Submit a signed statement that Nastech Pharmaceutical Company, Inc. has a licensing agreement with the patent owner, if applicable.

10. Submit a signed statement from the patent owner that it consents to an immediate effective date upon approval of this application.

Additionally, we have reevaluated the referenced NDA 19-722 Nascobal (cyanocobalamin) Nasal Gel and have determined that it should have been classified as submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Therefore, we consider NDA 21-642 to have been submitted pursuant to section 505(b)(2).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Holly Wieland at (301) 827-6410.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Enid Galliers
3/2/04 10:12:51 AM

2/25/04

NDA FILEABILITY CHECKLIST

NDA Number: 21-642
Applicant: Nastech Pharmaceutical Company, Inc.
Letter Date: Dec-29-2003
Drug Name: Nascobal® (Cyanocobalamin, USP) Spray

1. Is the CMC Section of the Application Fileable? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		Vol. 1.1, Attachment A
5	Is a statement provided that all facilities are ready for GMP inspection?	X		Jan-27 2004 e-mail (from Gordon Brandt to Holly Wieland)
6	Has an environmental assessment report or categorical exclusion been provided?	X		Vol. 1.2, p. 2 The applicant claims 21 CFR 25.31(b)
7	Does the section contain controls for the drug substance?	X		Cross-reference to DMF — (LOA dated Oct-07-2003 from — — provided in Vol. 1.2, p. 3)
8	Does the section contain controls for the drug product?	X		Vol. 1.3, pp. 248-250 Drug product release specifications (test method and acceptance criteria)
9	Has stability data and analysis been provided to support the requested expiration date?	X		Vol. 1.4, pp. 366-411 and Vol. 1.5
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	N/A
11	Have draft container labels been provided?		X	
12	Has the draft package insert been provided?	X		Vol. 1.1, pp. 45-58
13	Has an investigational formulations section been provided?	X		Vol. 1.2, pp. 42-63
14	Is there a Methods Validation package?	X		Vol. 1.3, pp. 346-460 and Vol. 1.4
15	Is a separate microbiological section included?		X	N/A

Review Chemist: Yvonne Yang, Ph.D. Date: Feb-09-2004
Team Leader: Mamta Gautam-Basak, Ph.D.
cc:
Original NDA 21-642
HFD-510/Division File
HFD-510/Chem/Y Yang/M Gautam-Basak
HFD-510/PM/H Wieland

NDA Number: 21-642
Applicant: Nastech Pharmaceutical Company, Inc.
Drug Name: Nascobal® (Cyanocobalamin, USP) Spray

2. Stability Data Required For Fileability:

	Stability Data Required	Yes	No
1	Does the NDA include 12 or more months of stability data?	✓	
2	Does the stability data cover the expiry date?		✓
3	Does the stability data include only the largest & smallest container sizes?	Only one size	
4	Does the stability data include all package sizes?	X	
5	Are there tabular data for each size and batch?	X	
6	Are there graphical data for each size and batch?	X	
7	Is a statistical consult required?		X
8	Is a stability protocol included?	X	
9	Are the stability indicating assays described?	X	
10	Is there the three point stability commitment?	X (Volume 1.4, page 385)	

3. Have all DMF References been Identified?

DMF No.	Holder	Description	LOA Included	Status
			Oct-07-2003	Adequate CMC Review #5 Dated Sept-04-2003 (Guoping Sun)
			Oct-27-2003	Adequate (5-ml vial) CMC Review #1 Dated Nov-17-2003 (Elsbeth Chikhale)
			Oct-15-2003	Need volume/page information regarding specific item to be reviewed
			Oct-17-2003	Adequate CMC Review Dated Jan-24-2003 (Raymond Frankewich)
			Oct-10-2003	Need volume/page information regarding specific item to be reviewed

Draft Information Request to be Included in the 74-Day Filing Review Letter:

- Footnotes for Table P.5.1-1 (page 249) and Table P.5.2-1 (page 250) indicate inconsistency in spray performance characterization testing. The testing for pump delivery, spray pattern, and droplet size distribution should be performed for routine release testing of the drug product. The proposed regulatory drug product specifications should be revised to include pump delivery, spray pattern, and droplet size distribution.

- The Letters of Authorization (LOA) for DMF — nd DMF — are incomplete. Please provide volume and page number for the specific item referenced in the DMF. Revised LOAs with the requested information should be submitted.

- Please provide representative HPLC chromatograms for Assay / Impurities and Degradation Products, at — time points, for stability testing at the accelerated condition (40°C/75% RH).

- Please provide detailed container/closure component information for container/closures used in the stability studies listed in Table P.8.3-1 (Volume 1.4, page 387).

- Please provide a sample of the nasal spray pump and the drug product for reference.

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

/s/

Yvonne Yang
2/24/04 01:56:56 PM
CHEMIST

Mamta Gautam-Basak
2/25/04 10:12:17 AM
CHEMIST
Concur, Fileable from CMC standpoint

~~3/9/04~~ 2/24/04

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-642

Trade Name: Nascobal Nasal Spray
Generic Name: cyanocobalamine
Strengths: 500mcg/0.1 mL

Applicant: Nastech Pharmaceutical Company Inc.

Date of Application: December 26, 2003
Date of Receipt: December 29, 2003
Date clock started after UN: NA
Date of Filing Meeting: February 9, 2004
Filing Date: February 27, 2004
Action Goal Date (optional): September 29, 2004
User Fee Goal Date: October 29, 2004

Indication(s) requested: Maintenance of normal hematologic status in pernicious anemia patients

Type of Original NDA: (b)(1) ___x_____ (b)(2) _____ X changed to (b)(2)(see attac
OR
Type of Supplement: (b)(1) _____ (b)(2) _____ ~~2/2~~ 3/
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? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___3_____
Other (orphan, OTC, etc.) _____

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

Form 3397 (User Fee Cover Sheet) submitted: YES x NO
User Fee ID # ___4528_____
Clinical data? YES _____ NO, Referenced to NDA # _19-722_____

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

YES NO x

If yes, explain:

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

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)]?

YES NO

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

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

- Does the submission contain an accurate comprehensive index? YES x NO
- Was form 356h included with an authorized signature? YES x NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES x NO
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES x NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  A CD-ROM with electronic files was submitted on December 28, 2003 and contained case report tabulations (word format), proposed labeling (word format), an annotated package insert (word format), a cover letter (PDF format), and an application form (PDF format).

  Additional comments: A second CD-ROM with electronic files was submitted on January 15, 2004 to replace the original one. The second submission included all files including labeling in both word and PDF formats and the CFR tabulations in PDF format.

- If in Common Technical Document format, does it follow the guidance? N/A YES x NO

- Is it an electronic CTD? N/A YES x 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?
  A CD-ROM with electronic files was submitted on December 28, 2003 and contained case report tabulations (word format), proposed labeling (word format), an annotated package insert (word format), a cover letter (PDF format), and an application form (PDF format).

  Additional comments: A second CD-ROM with electronic files was submitted on January 15, 2004 to replace the original one. The second submission included all files including labeling in both word and PDF formats and the CFR tabulations in PDF format.

- Patent information submitted on form FDA 3542a? YES x NO

- Exclusivity requested? YES, ___years NO x
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

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

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

- Financial Disclosure forms included with authorized signature? YES x* NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.) ***Form #3454 only**

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES x NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES x NO
  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: None

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

- Pre-NDA Meeting(s)? Date(s) _____ NO x
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO x

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO x

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO x

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

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A x YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA x YES NO

Chemistry

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

- Establishment Evaluation Request (EER) submitted to DMPQ? YES x NO

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

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

- Name of listed drug(s) and NDA/ANDA #: NA changed; reference drug: s19-Nascob 6

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a change in dosage form, from a gel to a spray. (See memo 2-27-04 3-9-

- 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.)

  YES NO x

- 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).

  YES NO x

- 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).

  YES NO x

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature. None of those listed.

  ____ 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.

  ____ 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 NO x

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

    YES NO x

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES x NO

  - 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 YES NO x

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): NA

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

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

    YES NO

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

    IND # _____ NO

    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 YES NO

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

YES NO x

Attachment

{See appended electronic signature page}

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

02/24/04

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-642

Trade Name: Nascobal Nasal Spray
Generic Name: cyanocobalamine
Strengths: 500mcg/0.1 mL

Applicant: Nastech Pharmaceutical Company Inc.

Date of Application: December 26, 2003
Date of Receipt: December 29, 2003
Date clock started after UN: NA
Date of Filing Meeting: February 9, 2004
Filing Date: February 27, 2004
Action Goal Date (optional): September 29, 2004
User Fee Goal Date: October 29, 2004

Indication(s) requested: Maintenance of normal hematologic status in pernicious anemia patients

Type of Original NDA: (b)(1) ___x_____ (b)(2) _____
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? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___3_____
Other (orphan, OTC, etc.) _____

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

Form 3397 (User Fee Cover Sheet) submitted: YES x NO
User Fee ID # ___4528_____
Clinical data? YES _____ NO, Referenced to NDA # _19-722_____

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

YES NO x

If yes, explain:

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

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)]?

YES NO

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

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

- Does the submission contain an accurate comprehensive index? YES x NO
- Was form 356h included with an authorized signature? YES x NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES x NO
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES x NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  A CD-ROM with electronic files was submitted on December 28, 2003 and contained case report tabulations (word format), proposed labeling (word format), an annotated package insert (word format), a cover letter (PDF format), and an application form (PDF format).

  Additional comments: A second CD-ROM with electronic files was submitted on January 15, 2004 to replace the original one. The second submission included all files including labeling in both word and PDF formats and the CFR tabulations in PDF format.

- If in Common Technical Document format, does it follow the guidance? N/A YES x NO

- Is it an electronic CTD? N/A YES x 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?
  A CD-ROM with electronic files was submitted on December 28, 2003 and contained case report tabulations (word format), proposed labeling (word format), an annotated package insert (word format), a cover letter (PDF format), and an application form (PDF format).

  Additional comments: A second CD-ROM with electronic files was submitted on January 15, 2004 to replace the original one. The second submission included all files including labeling in both word and PDF formats and the CFR tabulations in PDF format.

- Patent information submitted on form FDA 3542a? YES x NO

- Exclusivity requested? YES, ___years NO x
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

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

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

- Financial Disclosure forms included with authorized signature? YES x* NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.) ***Form #3454 only**

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES x NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES x NO
  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: None

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

- Pre-NDA Meeting(s)? Date(s) _____ NO x
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO x

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO x

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO x

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

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A x YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA x YES NO

Chemistry

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

- Establishment Evaluation Request (EER) submitted to DMPQ? YES x NO

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

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

- Name of listed drug(s) and NDA/ANDA #: NA

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

- 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.)

  YES NO x

- 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).

  YES NO x

- 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).

  YES NO x

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature. None of those listed.

  ____ 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.

  ____ 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 NO x
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

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

    N/A YES x NO
  - 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 YES NO x

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

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    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 YES NO

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

YES NO x

Attachment

{See appended electronic signature page}

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 9, 2004

BACKGROUND: Nascobal Nasal Spray (cyanocobalamine) is a new formulation of another approved drug product, NDA 19-722, Nascobal Gel, approved November 5, 1996. Nascobal is a synthetic vitamin B_{12} used for the maintenance of normal hematologic status of patients with pernicious anemia.

ATTENDEES: Mary Parks, Mamta Gautam-Basak, Yvonne Yang, Karen Davis-Bruno, Indra Antonipillai, Hae-Young Ahn, Sang Chung, Andrea Slavin, Randy Hedin, Holly Wieland

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Mary Parks
Secondary Medical:	David Orloff
Statistical:	None
Pharmacology:	Karen Davis-Bruno
Secondary Pharmacology:	Indra Antonipillai
Chemistry:	Mamta Gautam-Basak
Secondary Chemistry:	Yvonne Yang
Environmental Assessment (if needed):	None
Biopharmaceutical:	Hae-Young Ahn
Secondary Biopharmaceutical:	Sang Chung
Microbiology, sterility:	None
Microbiology, clinical (for antimicrobial products only):	None
DSI:	Andrea Slavin
Regulatory Project Management:	Holly Wieland
Regulatory Project Management:	Randy Hedin

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

CLINICAL FILE __x_____ REFUSE TO FILE ___

- Clinical site inspection needed: YES NO x
- Advisory Committee Meeting needed? YES, date if known _____ NO x
- 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?

NA x YES NO

CLINICAL MICROBIOLOGY NA x_____ FILE _____ REFUSE TO FILE _____

STATISTICS	NA x	FILE _____	REFUSE TO FILE _____
BIOPHARMACEUTICS		FILE ___x____	REFUSE TO FILE _____

- Biopharm. inspection needed: YES x* NO

*Biopharm Inspection needed for 2 study sites, clinical and analytical.

PHARMACOLOGY	NA _____	FILE ___x____	REFUSE TO FILE _____

- GLP inspection needed: YES x NO

CHEMISTRY		FILE __x____	REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO x
- Microbiology YES NO x

ELECTRONIC SUBMISSION:

Any comments: A CD-ROM with electronic files was submitted on December 28, 2003 and contained case report tabulations (word format), proposed labeling (word format), an annotated package insert (word format), a cover letter (PDF format), and an application form (PDF format). A second CD-ROM with electronic files was submitted on January 15, 2004 to replace the original one. The second submission included all files including labeling in both word and PDF formats and the CFR tabulations in PDF format.

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.

___x____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Goal to have content from reviewers for 74-day letter to RPM by February 20, 2004.
- Goal to send out 74-day letter with comments by February 27, 2004.
- Goal to finish reviews with team leader sign-off is September 29, 2004.
- Goal to have action package circulating by October 6, 2004.
- Goal to have action package to Division Director on October 28, 2004.
- The User Fee Goal Date is October 29, 2004.

{See appended electronic signature page}

Holly Wieland, RN, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Holly Wieland
2/24/04 02:32:42 PM
CSO

Holly Wieland
2/24/04 02:35:16 PM
CSO

01/22/04
ack letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-642

Nastech Pharmaceutical Company, Inc.
Attention: Gordon Brandt, MD
Executive VP of Clinical and Medical Affairs
45 Davids Drive
Hauppauge, NY 11788

Dear Dr Brandt:

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: Nascobal (cyanocobalamin nasal spray) 500 mcg/0.1 mL

Review Priority Classification: Standard (S)

Date of Application: December 26, 2003

Date of Receipt: December 29, 2003

Our Reference Number: NDA 21-642

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 February 27, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 29, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until February 27, 2006. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the

date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

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/Courier/Overnight Mail
Center for Drug Evaluation and Research
Division of Endocrine and Metabolic Drug Products (HFD 510)
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6410.

Sincerely,

{See appended electronic signature page}

Holly Wieland, R.N., M.P.H.,
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation, II
Center for Drug Evaluation and Research

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

/s/

Holly Wieland
1/22/04 05:21:15 PM

Reference is made to the teleconference of 1 November 2001 between Agency representatives and Nastech regarding the development plan and regulatory requirements for the marketing application of a new nasal dosage form of intranasal cyanocobalamin, Nascobal® Nasal Spray. During this teleconference, the Agency advised that one bioequivalence study comparing the nasal spray to the approved nasal gel (NDA 19-722) and intramuscular cyanocobalamin would be adequate to submit for approval of the nasal spray. Appended is completed form FDA 3454 pertaining to the bioequivalency study (Protocol No. C02-016). Please note that the clinical studies performed in support of NDA 19-722 are being referenced in support of this NDA and that all of the studies associated with the Nascobal® gel NDA predate the effective date of the regulation regarding financial disclosure by clinical investigators (21 CFR Part 54).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

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

Please mark the applicable checkbox.

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

Clinical Investigators		

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

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

NAME	TITLE
Gordon Brandt, M.D.	Executive Vice President of Science and Clinical Development
FIRM/ORGANIZATION	
Nastech Pharmaceutical Company Inc.	
SIGNATURE	DATE
Gordon Brandt MD	12/17/2003

Paperwork Reduction Act Statement

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

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

Created by: PSC Media Arts (301) 443-1090 EF

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS

Nastech Pharmaceutical Co., Inc.
45 Davids Drive
Hauppauge, NY 11788

2. TELEPHONE NUMBER *(Include Area Code)*

(631) 273-0101

3. PRODUCT NAME

Nascobal (Cyanocobalamin, USP)
Nasal Spray

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA #21-642

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4528

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Peter C. Apuzzi, R.Ph.	Vice President, Regulatory & Quality Affairs	4/11/03

FORM FDA 3397 (4/01)

C

7 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

12-05-01
(pre NDA / other - meeting)

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 1, 2001

TIME: 3:30 pm

LOCATION: 14B-45

APPLICATION: NDA 19-722

DRUG: Nascobal (Cyanocobalamin, USP) Nasal Gel

TYPE OF MEETING: T/Con

FIRM: Nastech Inc.

MEETING CHAIR: Mary Parks, M.D., Deputy Director

MEETING RECORDER: Steve McCort, Project Manager

FDA ATTENDEES

Name of FDA Attendee	Title	Division Name & HFD#
1. Mary Parks, M.D.	Deputy Director	DMEDP, HFD-510
2. Jean Temeck, M.D.	Medical Reviewer	DMEDP, HFD-510
3. Karen Davis-Bruno, Ph.D.	Pharmacology Supervisor	DMEDP, HFD-510
4. Hae-Young Ahn, Ph.D.	Biopharmaceutics Team Leader	OCPB, HFD-870
5. Sang M. Chung, Ph.D.	Biopharmacuetics Reviewer	OCPB, HFD-870
6. David Lewis, Ph.D.	Chemistry Reviewer	DNDC II, HFD-820
9. Sheldon Markofsky, Ph.D.	Acting Chemistry Team Leader	DNDC II, HFD-820
10. Neal Sweeney, Ph.D..	Microbiology Reviewer	OPS, HFD-805
11. Enid Galliers	Chief, Project Mang. Staff	DMEDP, HFD-510
12. Steve McCort	Regulatory Project Manager	DMEDP, HFD-510

NASTECH PARTICIPANTS

Attendee	Title	Sponsor/Firm Name
Peter Aprile, R. Ph.	Senior Director Regulatory and Quality Affairs	Nastech Pharm.
Jorge deMeireles, M.S.	Senior Director, Analytics	Nastech Pharm.
Anthony Sileno, M.S.	Senior Director Clinical Trials and Toxicology	Nastech Pharm.
Dilip Worah	Chief Scientific Officer	Nastech Pharm.
David Wormuth	Senior Vice President, Operation	Nastech Pharm.

BACKGROUND:

In a letter dated October 2, 2001, and received October 3, 2001, the firm requested a teleconference to discuss a plan for developing adequate data to support an NDA supplement to approved NDA 19-722 Nascobal or a new NDA for a new dosage form. Nascobal is currently approved as nasal gel for administering Vitamin B-12. The firm wishes to market cyanocobalamin as a nasal spray.

In addition the firm proposes making additional changes to the Nascobal product which include:

1. Changing the size of the container from a 5 mL Type I amber glass bottle to a 3 mL Type I amber glass bottle.
2. Changing the actuator from one designed to deliver 500 mcg cyanocobalamin/0.1 mL gel to one designed to deliver a 500 mcg spray.
3. Changing the indication statement in the labeling to combine elements of the existing Nascobal labeling with some additions.

The firm was granted the teleconference.

MEETING OBJECTIVE:

To discuss the development plan and regulatory requirements for submission of either a supplement to the approved NDA 19-722, Nascobal, or as a new drug application (NDA) for the new nasal spray dosage form.

DISCUSSION AND CONCLUSIONS:

The teleconference responded to the following questions (in a bold type) submitted in the October 19, 2001, meeting package.

FDA SUBMISSION REQUIREMENTS

1. **The sponsor proposes that the changes described herein be considered as a supplement to the current Nascobal NDA. Does FDA agree with this approach?**

   FDA Response:

   Since the Nasal Spray Solution proposed is a new dosage form, it would require the submission of a new NDA.

LABELING

2. **The proposed labeling has been revised to combine elements of the existing Nascobal label with those from labeling for the cyanocobalamin injection product.**

   The conditions associated with vitamin B_{12} deficiency that are listed in the proposed labeling are well documented. Similarly, the treatment endpoint of raising the plasma levels of cyanocobalamin for these conditions is well documented. The sponsor is proposing to perform pharmacokinetic profiling studies in cyanocobalamin naïve patients to determine whether the proposed product can elevate and maintain cyanocobalamin levels. Does FDA agree that if the results of such studies demonstrate that cyanocobalamin levels can be raised to and be maintained at adequate levels in this patient population these labeling changes can be implemented based upon the results of the clinical testing described above?

   FDA Response:

   The proposed labeling for the cyanocobalamin spray (as indicated on page 3 of the October 19, 2001, meeting package) is acceptable provided that the firm:

   1. Submits pertinent literature that demonstrates that patients with HIV or Crohn's disease are additional examples of vitamin B_{12} deficiency states.

   2. Submits a bioequivalence study which compares the approved nasal gel with the nasal solution to support the new NDA. The details of such a study are spelled out in the FDA response to "CLINICAL TRIALS," question #1.

The literature concerning use by post-menopausal women submitted in the meeting package is not adequate to support the changes in the labeling. (Note: The firm did not include any labeling statements for this population in their proposed labeling.)

1.

Does FDA agree that to support the revised labeling?

FDA Response:

The : are not necessary to support the changes in labeling for both Crohn's disease and HIV patients who are vitamin B_{12} deficient. Submission of representative articles from the literature and performance of a bioequivalence study comparing the nasal gel to the nasal spray solution would be adequate. The Agency suggests a three-way crossover pharmacokinetic study which compares IM injection, nasal gel, and the nasal spray in normal healthy adults.

STABILITY

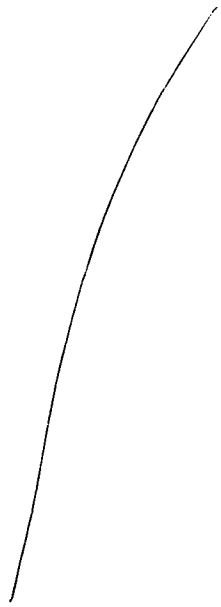
D

2 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling



OTHER ISSUES AND COMMENTS

1. For Pharmacology/Tox requirements the sponsor should submit adequate literature to support the safety of the drug product. If impurities are found during the stability testing for the drug product, the sponsor should address the issue in accordance with ICH guidances Q3A and Q3B.

2. Microbiological testing should include ——

3. The sponsor should be aware that they may need to pay user fees at the time of submission.

4. Comments regarding the need for the bioequivalence study have been made previously under CLINICAL TRIALS, question #1. The bioequivalence study protocol should be submitted to the existing IND for Nascobal.

5.

6.

ACTIONS:

1. The required bioequivalence study protocol will be submitted to the active IND for Nascobal gel.

2. The sponsor will submit a labeling supplement to the existing NDA 19-722 for Nascobal (Cyanocobalamin, USP) Nasal Gel.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

There are no unresolved issues at this time.

Minutes Preparer: _____
Steve McCort, Project Manager

Chair Concurrence: _____
Mary Parks, M.D., Dep. Dir.

POST MEETING ADDENDUM (to be communicated to the sponsor)):

, published literature is sufficient to support the proposed labeling changes provided that B_{12} therapy (either IM or nasal gel) is demonstrated to correct the vitamin B_{12} deficiency associated with Crohn's disease or AIDS.

Concurrence: E Galliers11.13, 27, 28 29/12/03/01/ J Temeck 11/11/.11/30/12/301/D Lewis 11/10, 19/01/ S Markofsky /11/.19.01/S Chung 11.20.01/H Ahn 11.21.01/K D Bruno 11.14.01/ N Sweeney 11/.21/01/M Parks 12/03, 04/01

cc: Original
HFD-19-722
HFD-510/Meeting Minutes files
HFD- 510/RM/SMcCort
HFD- 510/MParks/JTemeck/KDavis- Bruno/HAhn/SChung/Dlewis SMarkofsky/EGalliers/NSweeney

Drafted by: smm/November 10, 2001
Revised by: smm/ November 23, 2001
Revised by:smm/November 28, 2001
Revised by smm/December 3, 2001
Revised by:smm/December 3, 2001
final: smm/December 3, 2001

MEETING M INUTES

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

/s/

Mary Parks
12/5/01 02:39:52 PM