

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-102**

**ADMINISTRATIVE and  
CORRESPONDENCE  
DOCUMENTS**

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### 1.3.5 Patent and Exclusivity

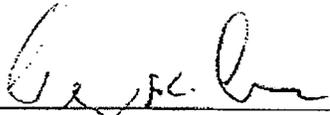
#### 1.3.5.1 Patent Information

In the opinion and to the best knowledge of Fleming and Company, there are not patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Per 21 CFR 314.50(h) and 21 CFR 314.53, patent information is submitted for the 505(b)(2) for \_\_\_\_\_ Nasal Spray. The undersigned hereby declares that Fleming & Company, Pharmaceuticals, does not claim any currently issued patents for the \_\_\_\_\_ Nasal Spray NDA.

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Form FDA 3542a is attached.



\_\_\_\_\_  
George F.C. Love  
Director of Legal and Regulatory Affairs  
Fleming & Company, Pharmaceuticals  
Fenton, MO

9/5/06

\_\_\_\_\_  
Date

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|   |   |
|---|---|
| Department of Health and Human Services<br>Food and Drug Administration<br><br><b>PATENT INFORMATION SUBMITTED WITH THE<br/>         FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b><br><br><i>For Each Patent That Claims a Drug Substance<br/>         (Active Ingredient), Drug Product (Formulation and<br/>         Composition) and/or Method of Use</i> | Form Approved: OMB No. 0910-0513<br>Expiration Date: 07/31/06<br>See OMB Statement on Page 3. |
|   | NDA NUMBER<br>022-102<br>NAME OF APPLICANT / NDA HOLDER<br>Fleming & Company, Pharmaceuticals |

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)  
 Nasal Spray

|   |   |
|---|---|
| ACTIVE INGREDIENT(S)<br>Cyanocobalamin, USP | STRENGTH(S)<br>25 mcg/0.1mL (50 mcg daily dose) |
|---|---|

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) |

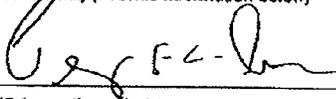
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  Yes  No

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

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|   |  |
|---|--|
| <b>For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.</b>  |  |
| <b>2. Drug Substance (Active Ingredient)</b>  |  |
| 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  | <input type="checkbox"/> Yes <input type="checkbox"/> No   |
| 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?   | <input type="checkbox"/> Yes <input type="checkbox"/> 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).   | <input type="checkbox"/> Yes <input type="checkbox"/> 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.)  |  |
| <input type="checkbox"/> Yes <input type="checkbox"/> No  |  |
| 2.6 Does the patent claim only an intermediate?   |  |
| <input type="checkbox"/> Yes <input type="checkbox"/> 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.)  |  |
| <input type="checkbox"/> Yes <input type="checkbox"/> No  |  |
| <b>3. Drug Product (Composition/Formulation)</b>  |  |
| 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?   |  |
| <input type="checkbox"/> Yes <input type="checkbox"/> No  |  |
| 3.2 Does the patent claim only an intermediate?   |  |
| <input type="checkbox"/> Yes <input type="checkbox"/> 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.)  |  |
| <input type="checkbox"/> Yes <input type="checkbox"/> No  |  |
| <b>4. Method of Use</b>   |  |
| <b>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:</b>   |  |
| 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?   |  |
| <input type="checkbox"/> Yes <input type="checkbox"/> 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? |
|   | <input type="checkbox"/> Yes <input type="checkbox"/> 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.)   |
|   |  |
| <b>5. No Relevant Patents</b>   |  |
| 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. |  |
| <input checked="" type="checkbox"/> Yes   |  |

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|  |   |
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| <b>6. Declaration Certification</b>  |   |
| <p>6.1 <i>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.</i></p> <p><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></p>  |   |
| 6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)  | Date Signed   |
|   | 9/5/06  |
| <p>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).</p>   |   |
| Check applicable box and provide information below.  |   |
| <input type="checkbox"/> NDA Applicant/Holder  | <input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| <input type="checkbox"/> Patent Owner  | <input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official           |
| Name<br>George F. C. Love  |   |
| Address<br>1733 Gilsinn Lane   | City/State<br>Fenton, MO  |
| ZIP Code<br>63026  | Telephone Number<br>636-343-5306  |
| FAX Number (if available)<br>636-343-5322  | E-Mail Address (if available)<br>glove@flemingcompany.com   |
| <p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration<br/>                 CDER (HFD-007)<br/>                 5600 Fishers Lane<br/>                 Rockville, MD 20857</p> <p style="text-align: center;"><i>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.</i></p> |   |

6/25/07

### PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-102 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: September 27, 2006 PDUFA Goal Date: July 27, 2007

HFD 510

Trade and generic names/dosage form: cyanocobalamin, USP, 25 mcg/0.1 mL nasal spray (trade name TBD)

Applicant: Fleming & Company, Pharmaceuticals

Therapeutic Class: Vitamins (other than D)

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): NA

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Daily maintenance therapy for vitamin B12 deficiency anemia following stabilization of plasma vitamin B12 levels by intramuscular injections

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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

- Yes: Please proceed to Section A.
- No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

#### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: Product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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.*

NDA 22-102

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

**Jennifer Johnson**

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

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

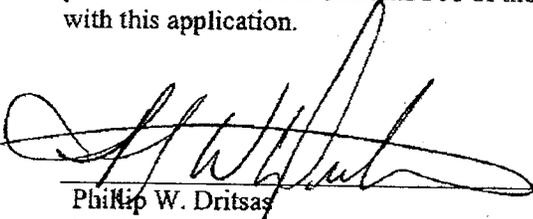
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Jennifer Johnson

6/25/2007 03:57:20 PM

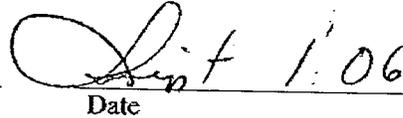
### 1.3.3 Debarment Certification

#### *Debarment Certification (FD&C Act 306(k)(1))*

Pursuant to Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act ("the Act"), as amended by the Generic Drug Enforcement Act of 1992, Fleming & Company, Pharmaceuticals (Fleming), hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Sections 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Philip W. Dritsas  
President  
Fleming & Company, Pharmaceuticals  
Fenton, MO



Date

b(4)

### 1.3.4 Financial Certification and Disclosure

Per 21 CFR 54.4, included herewith is the name of the clinical investigator who conducted the clinical bioequivalence study, PR99-063, in association with this 505(b)(2) New Drug Application for \_\_\_\_\_ Nasal Spray (Cyanocobalamin, USP). The protocol number, protocol title, and site address are also included below.

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A completed form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) is included herein regarding the financial interests and arrangements of the listed investigator.

In addition, a signed form from the investigator is included.

Protocol No.:

Protocol Title:

Site Address:

Investigator/Subinvestigators:

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|  |  |                        |   |  |               |                 |  |  |  |  |
|--|--|------------------------|---|--|---------------|-----------------|--|--|--|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>Food and Drug Administration<br><b>CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS</b>  | Form Approved: OMB No. 0910-0396<br>Expiration Date: April 30, 2009. |                        |   |  |               |                 |  |  |  |  |
| <b>TO BE COMPLETED BY APPLICANT</b>  |  |                        |   |  |               |                 |  |  |  |  |
| 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.   |  |                        |   |  |               |                 |  |  |  |  |
| <p><input checked="" type="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).</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 10%; text-align: center; vertical-align: middle;">Clinical Investigators</td> <td style="width: 50%; height: 20px;">_____</td> <td style="width: 40%;"></td> </tr> <tr> <td></td> <td style="height: 20px;"></td> <td></td> </tr> <tr> <td></td> <td style="height: 20px;"></td> <td></td> </tr> </table> |  | Clinical Investigators | _____   |  |               |                 |  |  |  |  |
| Clinical Investigators   | _____  |                        |   |  |               |                 |  |  |  |  |
|  |  |                        |   |  |               |                 |  |  |  |  |
|  |  |                        |   |  |               |                 |  |  |  |  |
| <p><input type="checkbox"/> (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)).</p>   |  |                        |   |  |               |                 |  |  |  |  |
| <p><input type="checkbox"/> (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.</p>   |  |                        |   |  |               |                 |  |  |  |  |
| <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px;">NAME<br/>Phillip W. Dritsas</td> <td style="width: 50%; padding: 2px;">TITLE<br/>President</td> </tr> <tr> <td colspan="2" style="padding: 2px;">FIRM / ORGANIZATION<br/>Fleming &amp; Company, Pharmaceuticals</td> </tr> <tr> <td style="padding: 2px;">SIGNATURE<br/></td> <td style="padding: 2px;">DATE<br/>7/17/06</td> </tr> </table>   | NAME<br>Phillip W. Dritsas   | TITLE<br>President     | FIRM / ORGANIZATION<br>Fleming & Company, Pharmaceuticals |  | SIGNATURE<br> | DATE<br>7/17/06 |  |  |  |  |
| NAME<br>Phillip W. Dritsas   | TITLE<br>President   |                        |   |  |               |                 |  |  |  |  |
| FIRM / ORGANIZATION<br>Fleming & Company, Pharmaceuticals  |  |                        |   |  |               |                 |  |  |  |  |
| SIGNATURE<br>  | DATE<br>7/17/06  |                        |   |  |               |                 |  |  |  |  |
| <p style="text-align: center;"><b>Paperwork Reduction Act Statement</b></p> <p>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:</p> <p style="text-align: right;">Department of Health and Human Services<br/>                 Food and Drug Administration<br/>                 5600 Fishers Lane, Room 14C-03<br/>                 Rockville, MD 20857</p>   |  |                        |   |  |               |                 |  |  |  |  |

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|   |                          |                                     |
|---|--------------------------|-------------------------------------|
| Name of Clinical Study:   | _____                    |                                     |
| Protocol Number:  | PR99-063                 |                                     |
| Sponsor Name:   | Fleming and Company      |                                     |
| Clinical Investigator:  | _____                    |                                     |
| Site Address:   | _____                    |                                     |
| Site Principal Investigator (if different from above):  |                          |                                     |
| Please review the following statements and provide the appropriate response with respect to the above-noted clinical study that you agreed to participate (these statements cover you, your spouse and each dependent child). (Reference: 21 CFR Part 54).<br>Note: Applies to compensation from Sponsor received either directly or indirectly.  |                          |                                     |
| <b>1. Compensation affected by the outcome of clinical studies</b><br>Was your financial compensation for participation in the clinical study affected by the outcome?<br>If "Yes", specify:  | Yes                      | No                                  |
|   | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
| <b>2. Significant equity interest in the sponsor of a covered study</b><br>(i) Did you have any ownership or equity interest in the Sponsor that exceeds USD \$50,000?<br>If "Yes", specify:<br><br>(ii) Did you have any ownership interest, stock options or other financial interest in the Sponsor whose value cannot be readily determined through reference to public prices?<br>If "Yes", specify: | Yes                      | No                                  |
|   | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
|   | Yes                      | No                                  |
|   | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
| <b>3. Proprietary interest in the tested product</b><br>Did you have any proprietary interest or other financial interest in the Sponsor's product including but not limited to: a patent, trademark, copyright or licensing agreement?<br>If "Yes", specify:   | Yes                      | No                                  |
|   | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
| <b>4. Significant payments of other sorts</b><br>Had you received, or entered into an agreement to receive, payments, grants, equipment or honoraria having a total monetary value exceeding USD \$25,000 from the Sponsor, excluding costs of conducting the current or other clinical studies?<br>If "Yes", specify:  | Yes                      | No                                  |
|   | <input type="checkbox"/> | <input checked="" type="checkbox"/> |

Fleming & Company, Pharmaceuticals  
Nasal Spray  
(Cyanocobalamin, USP)

New Drug Application  
NDA No. 022-102, Original  
2006

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|   |         |
|---|---------|
| I hereby certify that the information provided above is complete and accurate at the time of signing. |         |
|                      |         |
| Signature   | Date    |
|   | 6/17/05 |

## ACTION PACKAGE CHECKLIST

| Application Information   |                                      |  |
|---|--------------------------------------|--|
| BLA # N/A<br>NDA # 22-102   | BLA STN# N/A<br>NDA Supplement # N/A | If NDA, Efficacy Supplement Type N/A   |
| Proprietary Name: CaloMist<br>Established Name: cyanocobalamin, USP<br>Dosage Form: Nasal Spray, 25 mcg/0.1 mL  |                                      | Applicant: Fleming & Company, Pharmaceuticals  |
| RPM: Jennifer Johnson   |                                      | Division: DMEP (HFD-510)   Phone # 301-796-2194  |
| NDAs:<br>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)<br>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br><br>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) |                                      | 505(b)(2) NDAs and 505(b)(2) NDA supplements:<br>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):<br><br>NDA 21-642:<br>Nascobal (cyanocobalamin, USP) Nasal Spray, 500 mcg/0.1 mL<br><br>Provide a brief explanation of how this product is different from the listed drug.<br>This product has a lower strength of the active ingredient (cyanocobalamin, USP) than that of the innovator product.<br><br><input type="checkbox"/> If no listed drug, check here and explain:<br><br><b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b><br><br>X Confirmed <input type="checkbox"/> Corrected<br>Date: June 25, 2007 |
| ❖ User Fee Goal Date<br>❖ Action Goal Date (if different)   |                                      | July 27, 2007  |
| ❖ Actions   |                                      |  |
| • Proposed action   |                                      | X AP <input type="checkbox"/> TA <input type="checkbox"/> AE<br><input type="checkbox"/> NA <input type="checkbox"/> CR  |
| • Previous actions (specify type and date for each action taken)  |                                      | X None   |
| ❖ Advertising (approvals only)<br>Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews).   |                                      | X Requested in AP letter<br><input type="checkbox"/> Received and reviewed   |

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| ❖ Application Characteristics   |  |
| Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority<br>Chemical classification (new NDAs only): 5   |  |
| NDAs, BLAs and Supplements:<br><input type="checkbox"/> Fast Track<br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> CMA Pilot 1<br><input type="checkbox"/> CMA Pilot 2<br><br><input type="checkbox"/> Orphan drug designation |  |
| NDAs: Subpart H<br><input type="checkbox"/> Accelerated approval (21 CFR 314.510)<br><input type="checkbox"/> Restricted distribution (21 CFR 314.520)<br>Subpart I<br><input type="checkbox"/> Approval based on animal studies                      | BLAs: Subpart E<br><input type="checkbox"/> Accelerated approval (21 CFR 601.41)<br><input type="checkbox"/> Restricted distribution (21 CFR 601.42)<br>Subpart H<br><input type="checkbox"/> Approval based on animal studies |
| NDAs and NDA Supplements:<br><input type="checkbox"/> OTC drug  |  |
| Other:<br><br>Other comments: N/A   |  |
| ❖ Application Integrity Policy (AIP)  |  |
| • Applicant is on the AIP   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  |
| • This application is on the AIP  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  |
| • Exception for review ( <i>file Center Director's memo in Administrative Documents section</i> )   | <input type="checkbox"/> Yes <input type="checkbox"/> No N/A   |
| • OC clearance for approval ( <i>file communication in Administrative Documents section</i> )   | <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action   |
| ❖ Public communications (approvals only)  |  |
| • Office of Executive Programs (OEP) liaison has been notified of action  | <input type="checkbox"/> Yes <input type="checkbox"/> No   |
| • Press Office notified of action   | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  |
| • Indicate what types (if any) of information dissemination are anticipated   | <input checked="" type="checkbox"/> None<br><input type="checkbox"/> FDA Press Release<br><input type="checkbox"/> FDA Talk Paper<br><input type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other                      |

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

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

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| <p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p> |   |
| <b>Summary Reviews</b>  |   |
| ❖ Summary Reviews (e.g., Office Director, Division Director) ( <i>indicate date for each review</i> )   | Clinical Team Leader review<br>July 27, 2007                      |
| ❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) ( <i>indicate date</i> )  | N/A   |
| <b>Labeling</b>   |   |
| ❖ Package Insert  |   |
| <ul style="list-style-type: none"> <li>Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>  | July 18, 2007   |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>  | July 27, 2007   |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>   | September 26, 2006 (PLR format submitted January 22, 2007)<br>N/A |
| ❖ Patient Package Insert  |   |
| <ul style="list-style-type: none"> <li>Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>  | July 18, 2007   |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>  | July 27, 2007   |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>   | September 26, 2007 (PLR format submitted January 22, 2007)<br>N/A |
| ❖ Medication Guide  |   |
| <ul style="list-style-type: none"> <li>Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>  | N/A   |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>  | N/A   |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>  | N/A<br>N/A  |
| ❖ Labels ( <b>full color</b> carton and immediate-container labels)   |   |
| <ul style="list-style-type: none"> <li>Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>  | N/A   |
| <ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>   | July 27, 2007   |

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| ❖ Labeling reviews and minutes of any labeling meetings ( <i>indicate dates of reviews and meetings</i> ) | X DMETS July 13, 2007<br>X DSRCS May 25, 2007<br>X DDMAC July 6, 2007<br>X SEALD July 15, 2007<br>X Other reviews (RPM PLR format review) July 1, 2007<br><input type="checkbox"/> Memos of Mtgs N/A |
|---|--|

| <b>Administrative Documents</b>   |  |
|---|--|
| ❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )   | August 3, 2007   |
| ❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )   | <input type="checkbox"/> Included ( <b>Pending</b> )   |
| ❖ AIP-related documents <ul style="list-style-type: none"> <li>Center Director's Exception for Review memo</li> <li>If AP: OC clearance for approval</li> </ul>   | N/A<br>N/A   |
| ❖ Pediatric Page (all actions)  | X Included   |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> )   | X Verified, statement is acceptable  |
| ❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> <li>Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>Incoming submission documenting commitment</li> </ul>                                     | X None<br>N/A<br>N/A   |
| ❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)  | July 16, July 1, June 27, and May 17, 2007; December 8 and October 6, 2006   |
| ❖ Internal memoranda, telecons, email, etc.   | None   |
| ❖ Minutes of Meetings <ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>EOP2 meeting (<i>indicate date</i>)</li> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>   | N/A<br>X No mtg May 11, 2006 (meeting cancelled by sponsor – email responses sent on this date)<br>X No mtg<br>N/A |
| ❖ Advisory Committee Meeting <ul style="list-style-type: none"> <li>Date of Meeting</li> <li>48-hour alert or minutes, if available</li> </ul>  | X No AC meeting<br>N/A<br>N/A  |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)   | None   |
| <b>CMC/Product Quality Information</b>  |  |
| ❖ CMC/Product review(s) ( <i>indicate date for each review</i> )  | July 2, 2007<br>November 4, 2006   |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )   | X None   |
| ❖ BLAs: Product subject to lot release (APs only)   | <input type="checkbox"/> Yes <input type="checkbox"/> No N/A   |
| ❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <li>X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> </ul> | July 2, 2007 (Acceptable)  |

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|--|--|
| • <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )                               | N/A  |
| • <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> ) | N/A  |
| ❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )           | December 5, 2006<br><input type="checkbox"/> Not a parenteral product  |
| ❖ Facilities Review/Inspection   |  |
| ❖ NDAs: Facilities inspections (include EER printout)  | Date completed: March 29, 2007<br><input checked="" type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation |

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| ❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul> | N/A<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Accepted<br><input type="checkbox"/> Hold  |
| ❖ NDAs: Methods Validation   | <input checked="" type="checkbox"/> Completed<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Not yet requested<br><input type="checkbox"/> Not needed |

#### Nonclinical Information

|   |  |
|---|--|
| ❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )                      | June 7, 2007                                       |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> ) | <input checked="" type="checkbox"/> None           |
| ❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )                           | <input checked="" type="checkbox"/> No carc        |
| ❖ ECAC/CAC report/memo of meeting   | N/A  |
| ❖ Nonclinical inspection review Summary (DSI)   | <input checked="" type="checkbox"/> None requested |

#### Clinical Information

|   |  |
|---|--|
| ❖ Clinical review(s) ( <i>indicate date for each review</i> )   | July 3, 2007                                       |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review   | See clinical review (July 3, 2007)                 |
| ❖ Clinical consult reviews from other review disciplines/divisions/Centers ( <i>indicate date of each review</i> )              | <input checked="" type="checkbox"/> None           |
| ❖ Microbiology (efficacy) reviews(s) ( <i>indicate date of each review</i> )  | <input checked="" type="checkbox"/> Not needed     |
| ❖ Safety Update review(s) ( <i>indicate location/date if incorporated into another review</i> )                                 | N/A  |
| ❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> ) | N/A  |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date of each review</i> )                | <input checked="" type="checkbox"/> Not needed     |
| ❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )                                  | <input checked="" type="checkbox"/> None requested |
| • Clinical Studies  | N/A  |
| • Bioequivalence Studies  | N/A  |
| • Clin Pharm Studies  | N/A  |
| ❖ Statistical Review(s) ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None           |
| ❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None      June 21, 2007   |

## Appendix A to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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

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Jennifer Johnson  
8/3/2007 11:55:57 AM

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-102 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: \_\_\_\_\_  
Established Name: Cyanocobalamin Nasal Spray  
Strengths: 25 mcg/0.1 mL

b(4)

Applicant: Fleming & Company, Pharmaceuticals  
Agent for Applicant (if applicable): N/A

Date of Application: September 26, 2006  
Date of Receipt: September 27, 2006  
Date clock started after UN: N/A  
Date of Filing Meeting: November 14, 2006  
Filing Date: November 26, 2006  
Action Goal Date (optional): July 25, 2007

User Fee Goal Date: July 27, 2007

Indication(s) requested: Daily maintenance therapy for vitamin B-12 deficiency anemia following stabilization of plasma vitamin B-12 levels by IM injections

Type of Original NDA: (b)(1)  (b)(2) X  
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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 or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P   
Resubmission after withdrawal? N/A Resubmission after refuse to file? N/A  
Chemical Classification: (1,2,3 etc.) 5  
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES : X NO

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

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

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

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A  
YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

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

- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES  NO

2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

- Does the eNDA, follow the guidance? N/A  
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format? N/A

Additional comments: None

3. This application is an eCTD NDA. YES  NO   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments: None

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, 3 Years NO   
*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 . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?  
**(full waiver of pediatric requirements included)**  
YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO X  
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES X NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? 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 and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 58,346
- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO X  
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) N/A NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) Cancelled; email responses sent on May 11, 2006 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) N/A NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO X  
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO X

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: PLR was not submitted with the original submission on September 26, 2007. However, PLR was requested in the 74-day letter and submitted on January 22, 2007.

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES X NO
- Risk Management Plan consulted to OSE/IO? N/A X YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES  NO

**If Rx-to-OTC Switch or OTC application: N/A**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical (N/A)**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? 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 EA officer, OPS? YES  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team? YES X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 14, 2006

NDA #: 22-102

DRUG NAMES ~~\_\_\_\_\_~~ Nasal Spray (cyanocobalamin, USP) 25 mcg/0.1 mL

APPLICANT: Fleming & Company, Pharmaceuticals

BACKGROUND:

This drug is administered intranasally and is indicated for ~~\_\_\_\_\_~~. The sponsor is basing justification of approval of this 505(b)(2) application on the listed drug Nascobal (cyanocobalamin, USP) Nasal Spray, 500 mcg/0.1 mL (NDA 21-642, approved January 31, 2005).

The sponsor conducted an open-label study to evaluate the safety and efficacy of ~~\_\_\_\_\_~~ (referred to as ~~\_\_\_\_\_~~) in 25 patients who previously required intramuscular vitamin B12 injections to maintain normal serum B12 levels. These patients replaced their maintenance B12 injections with ~~\_\_\_\_\_~~ once daily (50 mcg daily dose of cyanocobalmin) for a period of 8 weeks.

The sponsor requested a pre-NDA meeting on February 28, 2006, (background package submitted on April 11, 2006) and received responses via electronic mail on May 11, 2006, in lieu of having a formal meeting.

ATTENDEES: William Lubas, Theresa Kehoe, Mary Parks, Hae Young Ahn, Sang Chung, Suong Tran, Karen Davis Bruno, Enid Galliers, Jennifer Johnson

ASSIGNED REVIEWERS (including those not present at filing meeting) :

**Discipline/Organization**

**Reviewer**

|   |                   |
|---|-------------------|
| Medical:  | William Lubas     |
| Secondary Medical:  | Theresa Kehoe     |
| Statistical:  | N/A               |
| Pharmacology:   | Karen Davis Bruno |
| Statistical Pharmacology:                                 | N/A               |
| Chemistry:  | Yvonne Yang       |
| Environmental Assessment (if needed):                     | N/A               |
| Biopharmaceutical:  | Sang Chung        |
| Microbiology, sterility:                                  | Vinayak Pawar     |
| Microbiology, clinical (for antimicrobial products only): | N/A               |
| DSI:  | N/A               |
| OPS:  | N/A               |

Regulatory Project Management:  
Other Consults:

Jennifer Johnson  
OSE (DMETS, DSRCS, DDMAC)

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

CLINICAL FILE X REFUSE TO FILE

• Clinical site audit(s) needed? YES  NO X  
If no, explain:

• Advisory Committee Meeting needed? YES, date if known N/A NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?  
N/A X YES  NO

CLINICAL MICROBIOLOGY N/A X FILE  REFUSE TO FILE

STATISTICS N/A X FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE X REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES  NO X

PHARMACOLOGY/TOX N/A  FILE X REFUSE TO FILE

• GLP audit needed? YES  NO X

CHEMISTRY FILE X REFUSE TO FILE

• Establishment(s) ready for inspection? YES X NO

• Sterile product? YES X NO

If yes, was microbiology consulted for validation of sterilization?  
YES X NO

**ELECTRONIC SUBMISSION:**

Any comments: N/A

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

The application is unsuitable for filing. Explain why:

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

No filing issues have been identified.

X Filing issues to be communicated by Day 74. List (optional): Letter issued on December 8, 2006

**ACTION ITEMS:**

- 1.X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
- 5.X Convey document filing issues/no filing issues to applicant by Day 74.

Jennifer Johnson  
Regulatory Project Manager

**APPEARS THIS WAY ON ORIGINAL**

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 21-642  
Nascobal (cyanocobalamin) Nasal Spray, 500 mcg/0.1 mL
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES  NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval 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? YES  NO

(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))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO
- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

(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," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

If "Yes," to (c), proceed to question 7.

**NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s): Nascobal Nasal Spray (cyanocobalamin)

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. Yes

8. 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").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that 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 may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO
13. 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.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 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)  
Patent number(s):

**NOTE:** 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)]. OND will contact you to verify that this documentation was received.

- 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).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 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)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES  NO

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

N/A  YES  NO

*Study PR99-063: Nasal Delivery of Vitamin B<sub>12</sub> (open-label study to evaluate daily intranasal administration of 50 mcg cyanocobalamin for 8 weeks in patients who previously have required IM vitamin B<sub>12</sub> injections to maintain normal serum B<sub>12</sub> levels)*

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

| Application No. | Product No. | Exclusivity Code | Exclusivity Expiration |
|-----------------|-------------|------------------|------------------------|
|                 |             |                  |                        |
|                 |             |                  |                        |
|                 |             |                  |                        |

APPEARS THIS WAY ON ORIGINAL

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

-----  
Jennifer Johnson  
8/3/2007 12:39:07 PM  
CSO

**fleming  
& company**  
PHARMACEUTICALS

ORIGINAL

N-000-BL

RECEIVED

JUL 27 2007

CDER White Oak DR 1

July 27, 2007

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705

RECEIVED

JUL 27 AM.

HFD-510/CDER

Re: **CaloMist<sup>®</sup> Nasal Spray (Cyanocobalamin, USP), 25 mcg/0.1mL**  
**505(b)(2) New Drug Application No. 022-102**  
**Amendment No. 0006: Labeling: Final Draft Labeling**

**Attention: Jennifer Johnson, Regulatory Project Manager**

Dr. Parks:

On behalf of Fleming & Company, Pharmaceuticals (Fleming) and pursuant to 21 CFR 314.60, we would like to amend the New Drug Application (NDA) referenced above and accepted for filing on December 10, 2006.

Reference is made to e-mail correspondences received by Fleming from the Division on June 27, July 1, July 10(2), July 16, July 18, July 20, and July 25(2), 2007. Reference is also made to a teleconference on July 13, 2007 between representatives of Fleming and the Division.

As requested, Fleming has revised the labeling accordingly. Included in this amendment is Final Draft Labeling of the Prescribing Information (PI) that complies with the new PLR formatting requirements, the carton label and the bottle label.

If there are any questions concerning this submission, please contact Christina Patullo, Regulatory Affairs Manager, at the following address:

Fleming & Company, Pharmaceuticals  
1733 Gilsinn Lane  
Fenton, MO 63026

Telephone: (636) 343-5306 x 333  
Facsimile: (636) 343-5322  
E-mail: [cpatullo@flemingcompany.com](mailto:cpatullo@flemingcompany.com)

PHARMACEUTICAL SPECIALTIES...  
PROMOTED ETHICALLY

1733 Gilsinn Lane  
Fenton, St. Louis County, MO 63026  
636-343-5306  
[www.flemingcompany.com](http://www.flemingcompany.com)

Mary Parks, M.D.

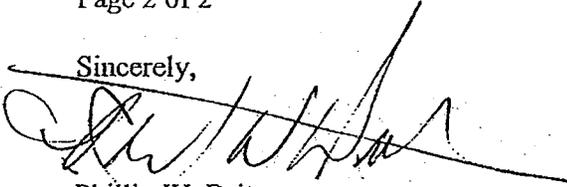
Re: CaloMist<sup>®</sup> Nasal Spray

505(b)(2) New Drug Application No. 022-102

Amendment No. 0006: Labeling: Final Draft Labeling

Page 2 of 2

Sincerely,

A handwritten signature in black ink, appearing to read "Phillip W. Dritsas", is written over a horizontal line. The signature is cursive and somewhat stylized.

Phillip W. Dritsas  
President

Enclosures

cc: C. Patullo, Fleming & Company, Pharmaceuticals

APPEARS THIS WAY ON ORIGINAL



July 26, 2007

**COPY BY E-MAIL/ORIGINAL BY MAIL**

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
White Oak CDER Office Building 22  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**RE: NDA #22-102, CALOMIST Nasal Spray (cyanocobalamin); Marketing Status Upon Approval**

Dear Dr. Parks:

We are writing to inform you that upon FDA's approval of the above-referenced NDA, Fleming does not plan to begin marketing the drug product immediately. As such, Fleming requests that the Agency identify CALOMIST (cyanocobalamin) Nasal Spray in FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") as a discontinued drug product. That is, upon approval of NDA #22-102, CALOMIST Nasal Spray should be included in the "Discontinued Drug Product List" instead of the "Prescription Drug Product List" section of the Orange Book. Fleming will notify FDA once the company begins marketing the drug product.

Ms. Mary Ann Holovac of FDA's Orange Book staff recommended that Fleming request, for administrative purposes, that the approval letter for NDA #22-102 include a statement acknowledging that Fleming does not intend to market CALOMIST Nasal Spray until further notice. Fleming therefore requests that any approval letter issued by the Division of Metabolism and Endocrinology Products for NDA #22-102 include such a statement.

Please contact me at 636.343.5306 ext. 260 if you have any questions or require additional information concerning this letter.

Sincerely,

/S/ George F.C. Love

George F.C. Love  
*Vice President of Legal &  
Regulatory Affairs*

cc: Mary Ann Holovac (by email)  
Director, Drug Information, FDA  
Jennifer Johnson (by email)  
Consumer Safety Officer, DMEP, FDA  
Michael Jones (by email)  
Office of Regulatory Policy, FDA

APPEARS THIS WAY ON ORIGINAL

**Johnson, Jennifer**

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**From:** Johnson, Jennifer  
**Sent:** Wednesday, July 25, 2007 6:30 PM  
**To:** 'Patullo, Chris'  
**Cc:** 'Love, George'; Johnson, Jennifer  
**Subject:** CaloMist Carton and Container Label Comments (DMETS and CMC)

Dear Chris and George,

Below are the comments regarding the revised carton and container labels for CaloMist Nasal Spray, NDA 22-102.

Please let me know if you have any questions or concerns.

Kind Regards,  
Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
**301-796-2194 phone**  
**301-796-9712 fax**  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

---

This memo is written in response to a request from the Division of Metabolism and Endocrinology Products for a review of the revised container label and carton labeling submitted for CaloMist Nasal Spray. DMETS acknowledges that you have addressed many of our recommendations presented in a previous label review (comments sent via email on July 16, 2007). We have reiterated the recommendations not identified in this revision and we have the following additional recommendations to further minimize user error and maximize patient safety. The chemistry reviewer concurrence and notes are listed in italics below each point below, where applicable.

**A. GENERAL COMMENTS**

---

**b(4)**

1   Page(s) Withheld

       Trade Secret / Confidential (b4)

  ✓   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

*Withheld Track Number: Administrative-  1*

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

-----  
Jennifer Johnson  
7/25/2007 06:33:34 PM  
CSO

7/19/07

|  |                          |
|--|--------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION | REQUEST FOR CONSULTATION |
|--|--------------------------|

|  |   |
|--|---|
| (Division/Office):<br><b>Director, Division of Medication Errors and Technical Support (DMETS), HFD-420<br/>         WO22, RM 4447</b> | FROM: Jennifer Johnson, RPM, Division of Metabolism and Endocrinology Products (DMEP), HFD-510, WO22, Rm 3393 |
|--|---|

|                       |         |                   |  |                         |
|-----------------------|---------|-------------------|--|-------------------------|
| DATE<br>July 19, 2007 | IND NO. | NDA NO.<br>22-102 | TYPE OF DOCUMENT<br>New NDA<br>(carton/container labels) | DATE OF DOCUMENT<br>N/A |
|-----------------------|---------|-------------------|--|-------------------------|

|   |                                    |  |  |
|---|------------------------------------|--|--|
| NAME OF DRUG<br>CaloMist Nasal Spray<br>(cyanocobalamin, USP),<br>25 mcg/0.1 mL | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>Vitamin other than D | DESIRED COMPLETION DATE<br>July 23, 2007 |
|---|------------------------------------|--|--|

NAME OF FIRM: Fleming & Company, Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

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

**II. BIOMETRICS**

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

**III. BIOPHARMACEUTICS**

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

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Please review the attached new carton and container color mock-up labels, submitted by the sponsor via email on July 19, 2007. The new trade name is incorporated. Feel free to contact me with any questions. Thanks! Jennifer

PDUFA DATE: July 27, 2007  
 ATTACHMENTS: Draft Package Insert, Container and Carton Labels  
 CC: Archival IND/NDA 22-102  
 HFD-510/Division File  
 FD-510/RPM  
 FD-510/Reviewers and Team Leaders

|  |  |
|--|--|
| NAME AND PHONE NUMBER OF REQUESTER<br><b>Jennifer Johnson (301) 796-2194</b> | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |
|--|--|

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/s/  
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Jennifer Johnson

7/19/2007 04:26:10 PM

Revised carton and container labels (with new trade name)

**Johnson, Jennifer**

---

**From:** Johnson, Jennifer  
**Sent:** Monday, July 16, 2007 1:12 PM  
**To:** 'Patullo, Chris'  
**Cc:** 'Love, George'; Johnson, Jennifer  
**Subject:** DMETS Labeling Review Comments  
**Attachments:** DMETS Comments to Sponsor.pdf

Dear Chris,

Attached is the portion of the DMETS review that includes the carton and container labeling comments.

The paragraph preceding section III is the end of the trade name review - nothing that you have to address, just that it was not possible to delete that portion from the review. Please let me know if you have any comments or questions.

Thanks!

Kind Regards,  
Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
301-796-2194 phone  
301-796-9712 fax  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

APPEARS THIS WAY ON ORIG

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/s/

-----  
Jennifer Johnson  
7/18/2007 02:11:36 PM  
CSO

7/18/07

# MEMORANDUM

To: Jennifer Johnson  
Division of Metabolism and Endocrinology Products

From: Iris Masucci, PharmD, BCPS  
Division of Drug Marketing, Advertising, and Communications  
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: July 15, 2007

Re: Comments on draft labeling for \_\_\_\_\_ (cyanocobalamin)  
NDA 22-102

b(4)

---

We have reviewed the proposed label for \_\_\_\_\_ (FDA version dated 7/10/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

## GENERAL COMMENTS

\_\_\_\_\_

b(4)

## HIGHLIGHTS

10 Page(s) Withheld

       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

-----  
Iris Masucci  
7/17/2007 10:32:58 AM  
DDMAC REVIEWER

Laurie Burke  
7/18/2007 08:19:40 PM  
INTERDISCIPLINARY

DFS 7/6/07

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**Memorandum**

**\*\*\*PRE-DECISIONAL AGENCY INFORMATION\*\*\***

**Date:** July 6, 2007

**To:** Jennifer Johnson, Regulatory Project Manager  
Division of Metabolic and Endocrine Products

**From:** Kanika Vij, Pharm.D.  
Division of Drug Marketing, Advertising, and Communications

**Subject:** Drug: \_\_\_\_\_ Nasal Spray (cyanocobalamin, USP)  
NDA: 22-102

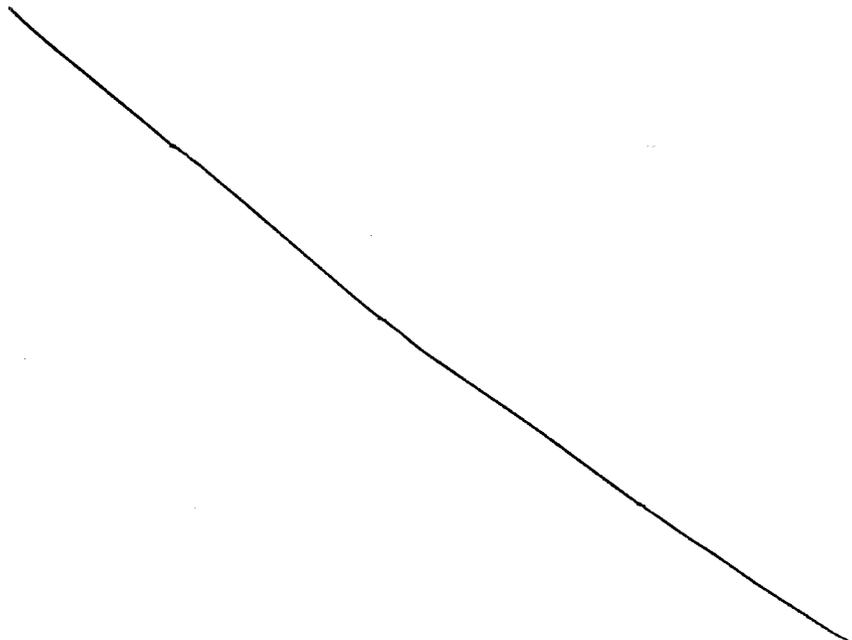
b(4)

DDMAC has reviewed proposed product labeling, patient labeling, and carton labeling for : \_\_\_\_\_ Nasal Spray (cyanocobalamin, USP) and we offer the following comments.

b(4)

If you have any questions or concerns regarding my comments, please contact me.

**Product Label**



b(4)

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/s/

-----  
Kanika Vij  
7/6/2007 01:11:10 PM  
DDMAC REVIEWER

**fleming  
& company**  
PHARMACEUTICALS

July 3, 2007

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705

Re: \_\_\_\_\_ Nasal Spray (Cyanocobalamin, USP), 25 mcg/0.1mL  
505(b)(2) New Drug Application No. 022-102  
Amendment No. 0005: Clinical and Labeling: Complete Response to the  
Clinical Reviewer's Request for Information (Dated May 17, 2007)

b(4)

**Attention: Jennifer Johnson, Regulatory Project Manager**

Dr. Parks:

On behalf of Fleming & Company, Pharmaceuticals (Fleming) and pursuant to 21 CFR 314.60, we would like to amend the New Drug Application (NDA) referenced above and accepted for filing on December 10, 2006.

As requested by the Division in their May 17, 2007, e-mail correspondence, and the subsequent correspondences on June 5, June 15, June 18, and June 19, 2007, the responses to the Clinical Reviewer request for information should be provided as an official amendment to our New Drug Application.

Accordingly, the responses are provided in this current submission.

This submission is provided as an electronic amendment and consists of one (1) volume containing the complete archival copy of the NDA amendment (1 CD-ROM) and paper copies of the following documents containing original signatures: cover letter and Form FDA 356h. Please note that documents containing original signatures are also provided in the electronic copy. Since this is an electronic submission, only one archival copy is provided.

The approximate size of the application is 7.55 MB. The CD-ROM has been scanned using the Symantec AntiVirus 10.0 software, and were found to be virus free.

In addition, in accordance with 21 CFR 314.94 and the Guidance for Industry entitled *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, we request that the Electronic Document Room forward a copy of this submission to the Food and Drug Administration District Office in Lenexa, KS.

PHARMACEUTICAL SPECIALTIES...  
PROMOTED ETHICALLY

1733 Gilsinn Lane  
Fenton, St. Louis County, MO 63026  
636-343-5306  
www.flemingcompany.com

Mary Parks, M.D.

Re: \_\_\_\_\_ Nasal Spray

505(b)(2) New Drug Application No. 022-102

Amendment No. 0005: Clinical and Labeling: Response to the Clinical Reviewer's Request  
for Information (Dated May 17, 2007)

Page 2 of 2

If there are any questions concerning this submission, please contact Christina Patullo,  
Regulatory Affairs Manager, at the following address:

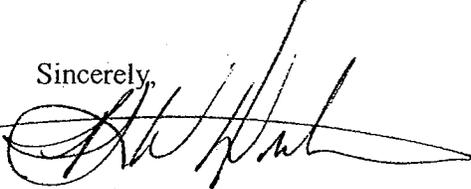
Fleming & Company, Pharmaceuticals  
1733 Gilsinn Lane  
Fenton, MO 63026

Telephone: (636) 343-5306 x 333

Facsimile: (636) 343-5322

E-mail: cpatullo@flemingcompany.com

Sincerely,



Phillip W. Dritsas  
President

Enclosures

cc: C. Patullo, Fleming & Company, Pharmaceuticals  
M. Whalon, Beckloff Associates, Inc.

APPEARS THIS WAY ON ORIGINAL

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

**REQUEST FOR CONSULTATION**

To (Office/Division): Kanika Vij, Division of Drug Marketing,  
Advertising and Communication, WO 22 Rm 1467  
(301) 796-1200

FROM (Name, Office/Division, and Phone Number of Requestor):  
Jennifer Johnson, RPM, Division of Metabolism and  
Endocrinology Products, WO 22 Rm 3393  
(301) 796-2194

|                      |         |                   |  |  |
|----------------------|---------|-------------------|--|--|
| DATE<br>July 1, 2007 | IND NO. | NDA NO.<br>22-102 | TYPE OF DOCUMENT<br>New NDA<br>505(b)(2) | DATE OF DOCUMENT<br>September 26, 2006<br>January 22, 2007 |
|----------------------|---------|-------------------|--|--|

|   |                                    |  |   |
|---|------------------------------------|--|---|
| NAME OF DRUG<br>Nasal Spray<br>(cyanocobalamin, USP)<br>25 mcg/0.1 mL | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>Vitamin (other than D) | DESIRED COMPLETION DATE<br>July 9, 2007 |
|---|------------------------------------|--|---|

NAME OF FIRM: Fleming & Company, Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input checked="" type="checkbox"/> DRUG ADVERTISING     | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

**II. BIOMETRICS**

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input checked="" type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES                | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW                   | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):            |   |

**III. BIOPHARMACEUTICS**

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

**IV. DRUG SAFETY**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the labeling submitted by the sponsor (carton/container labeling submitted with the original NDA on September 26, 2006, PLR PI/PPI submitted on January 22, 2007), located in the EDR. A proper Word copy of the PLR has not been submitted officially to the NDA; I will provide it to you via email. The trade name review by DMETS is still pending (preferred product names: 1. CaloMist Nasal Spray, 2.                     ). Please feel free to contact me with any questions or concerns. Many thanks, Jennifer

SIGNATURE OF REQUESTOR  
Jennifer Johnson

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

b(4)

b(4)

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/s/

-----  
Jennifer Johnson  
7/1/2007 03:37:23 PM

**Johnson, Jennifer**

---

**From:** Johnson, Jennifer  
**Sent:** Sunday, July 01, 2007 4:00 PM  
**To:** 'Patullo, Chris'  
**Cc:** Johnson, Jennifer  
**Subject:** NDA 22-102: PLR Labeling Format Review Comments  
**Attachments:** Labeling Format Review to Sponsor.doc

Dear Chris,

We have completed the initial format review of your proposed package insert for NDA 22-102. Please see the attached document listing our comments.

I did not include \_\_\_\_\_ Nasal Spray as the product trade name at the top of the document, as this is not the preferred trade name.

If possible, please revise and submit your updated proposed package insert by close of business on Thursday, July 5th.

Please contact me with any questions or concerns.

Many thanks,  
Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
**301-796-2194 phone**  
**301-796-9712 fax**  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

APPEARS THIS WAY ON ORIGINAL

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       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

-----  
Jennifer Johnson  
7/1/2007 04:03:48 PM  
CSO

**Johnson, Jennifer**

---

**From:** Johnson, Jennifer  
**Sent:** Wednesday, June 27, 2007 6:32 PM  
**To:** 'Patullo, Chris'  
**Cc:** Johnson, Jennifer  
**Subject:** Reviewer Comments: PPI (NDA 22-102)  
**Attachments:** dsrscs clean.doc; dsrscs marked.doc

b(4)

Dear Chris,

Attached is the Patient Instruction Sheet (Patient Package Insert, or PPI) reviewed by DSRCS (Division of Surveillance, Research and Communication Support, a division within the Office of Surveillance and Epidemiology, formerly the Office of Drug Safety). There are both clean and marked versions so that recommended changes can be clearly seen. Of course, further modifications may be made after receiving comments from DMETS regarding the product trade name.

Please let me know if you have any questions.

Kind Regards,  
Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
**301-796-2194 phone**  
**301-796-9712 fax**  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

DFS 5/25/07

**MEMORANDUM**

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

**DATE:** May 25, 2007

**TO:** Mary Parks, M.D., Director  
Division of Metabolic and Endocrine Products

**VIA:** Jennifer Johnson, Regulatory Project Manager  
Division of Metabolic and Endocrine Products

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support

**THROUGH:** Toni Piazza-Hepp, Pharm.D., Deputy Director  
Division of Surveillance, Research, and Communication Support

**SUBJECT:** OSE/DSRCS Review of the Patient Instructions for Use for \_\_\_\_\_  
Nasal Spray (cyanocobalamin, USP) 25 mcg/0.1 mL

b(4)

**Background and Summary**

Fleming and Company Pharmaceuticals submitted an NDA on September 26, 2006, for \_\_\_\_\_ t Nasal Spray (cyanocobalamin, USP) 25 mcg/0.1 mL, \_\_\_\_\_

b(4)

Submitted labeling included Prescribing Information and a Patient Instruction Sheet. Revised labeling (Full Prescribing Information of FPI) as required to comply with the Physicians Labeling Rule (PLR) was submitted January 22, 2007.

DSRCS was consulted to review the Patient Instruction Sheet.

**Comments and Recommendations**

\_\_\_\_\_

b(4)

3   Page(s) Withheld

       Trade Secret / Confidential (b4)

  ✓   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

Withheld Track Number: Administrative-   4

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/s/

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Jennifer Johnson  
6/27/2007 06:34:52 PM  
CSO

June 21, 2007

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Re: \_\_\_\_\_ Nasal Spray (Cyanocobalamin, USP), 25 mcg/0.1mL  
505(b)(2) New Drug Application No. 022-102  
Amendment No. 0004: Chemistry: Complete Response to The Chemistry Reviewer's  
Request for Clarification (Dated May 17, 2007)

Attention: Jennifer Johnson, Regulatory Project Manager

Dr. Parks:

Pursuant to 21 CFR 314.60, we would like to amend the New Drug Application (NDA) referenced above and accepted for filing on December 10, 2006.

Reference is made to the FDA e-mail correspondence dated May 17, 2007, and the subsequent correspondences on May 21, 2007, June 7, 2007 and June 8, 2007 in which it was clarified by the CMC reviewer that Table 3.2.P.1-1 should be amended in the next CMC correspondence to express the Benzalkonium Chloride, \_\_\_\_\_ content as \_\_\_\_\_ with all other expressions of quantity in this table adjusted proportionately.

Table 3.2.P.1-1 and the respective QOS Table 2.3.P.1-1 have been amended accordingly, and both of these tables along with the remainder of sections 3.2.P.1 and 2.3.P.1 are provided in this current submission.

As a result of the requested numerical adjustment in the stated Benzalkonium Chloride, \_\_\_\_\_ quantity, the stated content of Purified Water, USP was very slightly compensated to maintain the correct total ingredient content throughout these tables.

This electronic amendment consists of one volume containing the complete archival copy of the NDA amendment (1 CD-ROM) and paper copies of the following documents containing original signatures: cover letter and Form FDA 356h. Please note that documents containing original signatures are also provided in the electronic copy. Since this is an electronic submission, only one archival copy is provided.

PHARMACEUTICAL SPECIALTIES...  
PROMOTED ETHICALLY

1733 Gilsinn Lane  
Fenton, St. Louis County, MO 63026  
636-343-5306  
www.flemingcompany.com

b(4)

b(4)

b(4)

Mary Parks, M.D.

Re: \_\_\_\_\_ Nasal Spray  
505(b)(2) New Drug Application No. 022-102  
Amendment No. 0004 – Chemistry Amendment

Page 2 of 2

b(4)

The approximate size of the application is 1.41 MB. The CD-ROM has been scanned using the Symantec AntiVirus 10.0 software, and were found to be virus free.

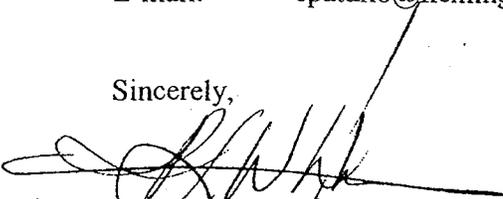
In addition, in accordance with 21 CFR 314.94 and the Guidance for Industry entitled *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, we request that the Electronic Document Room forward a copy of this submission to the Food and Drug Administration District Office in Lenexa, KS.

If there are any questions concerning this submission, please contact Christina Patullo, Regulatory Affairs Manager, at the following address:

Fleming & Company, Pharmaceuticals  
1733 Gilsinn Lane  
Fenton, MO 63026

Telephone: (636) 343-5306 x 333  
Facsimile: (636) 343-5322  
E-mail: [cpatullo@flemingcompany.com](mailto:cpatullo@flemingcompany.com)

Sincerely,



Phillip W. Dritsas  
President

Enclosures

cc: C. Patullo, Fleming & Company, Pharmaceuticals  
M. Whalon, Beckloff Associates, Inc.

OFS  
5/17/07

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

**REQUEST FOR CONSULTATION**

(Division/Office):  
**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
WO22, RM 4447**

FROM: Jennifer Johnson, Regulatory Project Manager  
DMEP, HFD-510, WO22, Rm 3393, 301-796-2194

DATE  
May 17, 2007

IND NO.

NDA NO.  
22-102

TYPE OF DOCUMENT  
NDA Amendment,  
505(b)(2)

DATE OF DOCUMENT  
January 22, 2007

NAME OF DRUG  
Nasal Spray  
(cyanocobalamin, USP)  
25 mcg/0.1 mL

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Vitamin

DESIRED COMPLETION DATE  
June 8, 2007

NAME OF FIRM: Fleming & Company, Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

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

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

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

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:  
Please see the January 22, 2007, amendment, located in the EDR. The sponsor wants to propose two trade names: 1) CaloMist Nasal Spray (cyanocobalamin, USP) and 2) Nasal Spray (cyanocobalamin, USP), as preferred alternatives to Nasal Spray (cyanocobalamin, USP).

Please feel free to contact me with any questions.

Thanks!  
Jennifer

PDUFA DATE: July 27, 2007  
ATTACHMENTS: Draft Package Insert, Container and Carton Labels

b(4)

b(4)

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/s/

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Jennifer Johnson  
5/17/2007 05:35:12 PM

**Johnson, Jennifer**

**From:** Johnson, Jennifer  
**Sent:** Thursday, May 17, 2007 4:06 PM  
**To:** 'Patullo, Chris'  
**Cc:** Johnson, Jennifer  
**Subject:** NDA 22-102: Clinical Reviewer Request for Information

Hi Chris,

Our clinical reviewer has some requests for information:

1. How were adverse events elicited during Study PR99-063? Were subjects given checklists or forms to complete at each visit? Were subjects questioned about adverse events at each visit, and if so, how?
2. Did the study personnel actively examine every patient's nasal mucosa at baseline and study end?
3. Why is one patient missing hematology data at Visit 6?
4. Why does Patient 511 have two sets of hematology data for Visit 1? Which set was used for analyses and how was this determination made?
5. Why does Patient 523 have hematology data for Visits 2 and 3?
6. Why are 1-2 patients missing vital sign data at Visit 6?
7. In your shift tables, you report that two patients had a shift in white blood cell count from normal to low. Besides Patient 501, who was the other patient who met this criteria?
8. Patient 511 has two screening vitamin B12 measurements, one of 176 pg/mL (07/07/2000) and another of 267 pg/mL (08/16/2000). Visit 2 occurred on 8/23/2000, which is only one week after the 267 pg/mL reading. Did the patient receive treatment with vitamin B12 between 07/07/2000 and 08/16/2000? How did you choose which screening measurement to use for the efficacy analyses?
9. You report that 12 patients did not have documentation of (1) the last date of their vitamin B12 injection, (2) their next scheduled injection, and/or (3) the frequency of their vitamin B12 injections. Provide the patient IDs for these 12 patients. For each patient, show which of the above documentation was missing. For these patients, how did you determine that Visit 1 corresponded to the midpoint between maintenance intramuscular injections and that Visit 2 corresponded to the time of the next scheduled vitamin B12 injection since the above documentation was missing?
10. For each of the 25 treated patients, provide the cause of the vitamin B12 deficiency, the duration of the vitamin B12 deficiency, and how the vitamin B12 deficiency was documented. **b(4)**
11. Why did Patient 525 receive \_\_\_\_\_ dosing through Week 11?
12. Were any investigators/subinvestigators other than Dr. Mark Dykewicz involved with this study? If yes, please submit financial disclosure information for these other individuals.
13. A few patients (e.g., 501, 502, and 514) had comparable vitamin B12 levels at Visits 1 and 2 (i.e., stable vitamin B12 levels at the time of the next scheduled intramuscular injection and just prior to \_\_\_\_\_ initiation). The Division cannot rule out the possibility that the vitamin B12 levels would have remained stable in these patients without the administration of \_\_\_\_\_. Please submit data from the literature showing the time course **b(4)**

5/17/2007

and magnitude of decline in vitamin B12 levels when patients on maintenance vitamin B12 injections do not receive their next scheduled vitamin B12 injection(s).

14. Please submit a Microsoft Word version of the PLR label.

15. Please present in tabular form the incidence of adverse events (by system-organ-class and preferred term) reported from Visit 1 up until the initiation of . \_\_\_\_\_ This information (although collected over a shorter time period than the treatment-emergent adverse events) will provide a background rate of adverse events that will help place the incidence of the treatment-emergent adverse events in perspective.

b(4)

Please submit responses to the above requests as an official amendment to your NDA.

Feel free to contact me with any questions or concerns.

Many thanks,

Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
301-796-2194 phone  
301-796-9712 fax  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

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/s/

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Jennifer Johnson  
5/17/2007 04:08:36 PM  
CSO

5/17/07

Page 1 of 1

**Johnson, Jennifer**

---

**From:** Johnson, Jennifer  
**Sent:** Thursday, May 17, 2007 3:50 PM  
**To:** 'Patullo, Chris'  
**Cc:** Johnson, Jennifer  
**Subject:** NDA 22-102: CMC Reviewer Request for Clarification

Hi Chris,

Our CMC reviewer has a request for clarification:

Please clarify the amount of benzalkonium chloride, — NF in the batch formula. The amount of benzalkonium chloride, — NF provided in the batch formulation (Table 3.2.P.3.2-1) is inconsistent with that provided in the drug product unit composition (Table 3.2.P.1-1). Provide your calculation for the amount in the batch formula.

b(4)

Thank you!

Kind Regards,  
Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
**301-796-2194 phone**  
**301-796-9712 fax**  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

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/s/

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Jennifer Johnson  
5/17/2007 03:54:43 PM  
CSO

**Johnson, Jennifer**

**From:** Joffe, Hylton  
**Sent:** Monday, March 19, 2007 8:26 PM  
**To:** Johnson, Jennifer; Slavin, Andrea  
**Cc:** Kehoe, Theresa  
**Subject:** RE: DSI Consult: \_\_\_\_\_ (NDA 22-102)

b(4)

Hi Jennifer and Andrea.

No need for DSI inspections for this NDA.  
Thanks for checking.

Hylton

---

**From:** Johnson, Jennifer  
**Sent:** Monday, March 19, 2007 2:15 PM  
**To:** Slavin, Andrea  
**Cc:** Joffe, Hylton  
**Subject:** DSI Consult: \_\_\_\_\_ : (NDA 22-102)

b(4)

Hi Andrea,

I received your message last week, inquiring as to whether or not DSI inspections would be required for \_\_\_\_\_ (NDA 22-102).

Bill Lubas, the former clinical reviewer, did not make a request that they be done.

Hylton Joffe has recently taken over as the clinical reviewer for \_\_\_\_\_ Hylton, do you agree with this assessment?

b(4)

Thanks much,  
Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
**301-796-2194 phone**  
**301-796-9712 fax**  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

APPEARS THIS WAY ON ORIGINAL

3/20/2007

March 15, 2007

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Re: \_\_\_\_\_ Nasal Spray (Cyanocobalamin, USP), 25 mcg/0.1 mL  
505(b)(2) New Drug Application No. 022-102  
Amendment No. 0003 – Stability Amendment

b(4)

Dr. Parks:

Pursuant to 21 CFR 314.60, we would like to amend the New Drug Application (NDA) referenced above and accepted for filing on December 10, 2006.

As agreed to with the Agency in their response to the pre-NDA CMC correspondence (Sections 1.6.3 and 3.2.R.4), and stated in the cover letter to the initial NDA, Fleming would submit twelve (12) months of ICH Q1A(R2) stability data for the three batches of the proposed commercial presentation during the initial NDA review period. As clarified by the Agency in their February 16, 2007, e-mail correspondence to Fleming, this information should be submitted cumulatively with all other ICH Q1A(R2) stability information previously submitted in the initial NDA.

Accordingly, the following stability data are provided in this current submission:

- Proposed commercial presentation:
  - Batch 0500314, 12 months at 25°C/60% RH (horizontal and upright orientations), 6 months at 40°C/75% RH (horizontal and upright orientations)
  - Batch 0500318, 12 months at 25°C/60% RH (horizontal and upright orientations), 6 months at 40°C/75% RH (horizontal and upright orientations)
  - Batch 0500326, 12 months at 25°C/60% RH (horizontal and upright orientations), 6 months at 40°C/75% RH (horizontal and upright orientations)
- Phase 3 clinical presentation:
  - Batch 9036, 75 months at 25°C/60% RH (horizontal orientation)
  - Batch 0060116, 63 months at 25°C/60% RH (horizontal orientation)

PHARMACEUTICAL SPECIALTIES...  
PROMOTED ETHICALLY

Mary Parks, M.D.

Re:            Nasal Spray

505(b)(2) New Drug Application No. 022-102

Amendment No. 0003 – Stability Amendment

Page 2 of 2

b(4)

This electronic amendment consists of one volume containing the complete archival copy of the NDA amendment (1 CD-ROM) and paper copies of the following documents containing original signatures: cover letter and Form FDA 356h. Please note that documents containing original signatures are also provided in the electronic copy. Since this is an electronic submission, only one archival copy is provided.

The approximate size of the application is 1.80 MB. The CD-ROM has been scanned using the Symantec AntiVirus 10.0 software, and were found to be virus free.

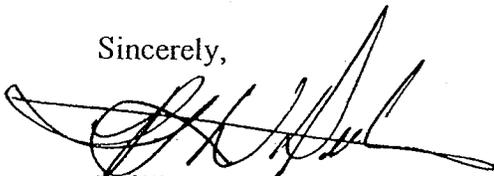
In addition, in accordance with 21 CFR 314.94 and the Guidance for Industry entitled *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, we request that the Electronic Document Room forward a copy of this submission to the Food and Drug Administration District Office in Lenexa, KS.

If there are any questions concerning this submission, please contact Christina Patullo, Regulatory Affairs Manager, at the following address:

Fleming & Company, Pharmaceuticals  
1733 Gilsinn Lane  
Fenton, MO 63026

Telephone: (636) 343-5306 x 333  
Facsimile: (636) 343-5322  
E-mail: cpatullo@flemingcompany.com

Sincerely,



Phillip W. Dritsas  
President

Enclosures

cc: C. Patullo, Fleming & Company, Pharmaceuticals  
M. Whalon, Beckloff Associates, Inc.

February 16, 2007

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Re: \_\_\_\_\_ Nasal Spray (Cyanocobalamin, USP), 25 mcg/0.1mL  
505(b)(2) New Drug Application No. 022-102  
Amendment No. 0002 – Clinical Pharmacology Amendment

b(4)

Dr. Parks:

Pursuant to 21 CFR 314.60, we would like to amend the New Drug Application (NDA) referenced above and accepted for filing on December 10, 2006.

Reference is made to the FDA Filing Communication dated 12/8/2006 in which the Agency requested we submit the following Clinical Pharmacology Information:

**Clinical Pharmacology:**

- 1. Your application contained no summary for the analytical methods and validation, and the summary is a required section for the study report even if the analytical method is a commercially available kit. Therefore, please submit the summary information or tell us its location if it has been submitted.**

**Response:**

A summary of each method and the corresponding validation is provided in this amendment.

This electronic amendment consists of one volume containing the complete archival copy of the NDA amendment (1 CD-ROM) and paper copies of the following documents containing original signatures: cover letter and Form FDA 356h. Please note that documents containing original signatures are also provided in the electronic copy. Since this is an electronic submission, only one archival copy is provided.

The approximate size of the application is 687 KB. The CD-ROM has been scanned using the McAfee Virus Scan Enterprise 7.1 software, with a virus definition date of February 16, 2007, and were found to be virus free.

PHARMACEUTICAL SPECIALTIES...  
PROMOTED ETHICALLY

Mary Parks, M.D.

Re:            Nasal Spray

505(b)(2) New Drug Application No. 022-102

Amendment No. 0002 – Clinical Pharmacology Amendment

Page 2 of 2

b(4)

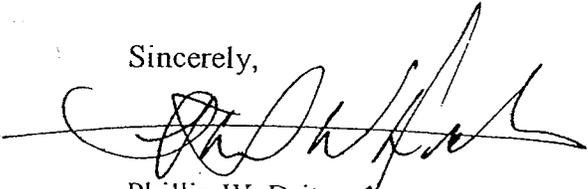
In addition, in accordance with 21 CFR 314.94 and the Guidance for Industry entitled *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, we request that the Electronic Document Room forward a copy of this submission to the Food and Drug Administration District Office in Lenexa, KS.

If there are any questions concerning this submission, please contact Christina Patullo, Regulatory Affairs Manager, at the following address:

Fleming & Company, Pharmaceuticals  
1733 Gilsinn Lane  
Fenton, MO 63026

Telephone: (636) 343-5306 x 333  
Facsimile: (636) 343-5322  
E-mail: cpatullo@flemingcompany.com

Sincerely,



Phillip W. Dritsas  
President

Enclosures

cc: C. Patullo, Fleming & Company, Pharmaceuticals  
M. Whalon, Beckloff Associates, Inc.

January 22, 2007

Mary Parks, M.D.  
Acting Director  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Re: \_\_\_\_\_ Nasal Spray (Cyanocobalamin, USP), 25 mcg/0.1mL  
505(b)(2) New Drug Application No. 022-102  
Serial No. 0001 – Labeling Amendment

b(4)

Dr. Parks:

Pursuant to 21 CFR 314.60, we would like to amend the New Drug Application (NDA) referenced above and accepted for filing on December 10, 2006.

Reference is made to the FDA Filing Communication dated 12/8/2006 in which the Agency requested we submit the following labeling information:

Labeling

2. All new drug applications submitted on or after June 30, 2006, are required to include Prescribing Information (PI) that complies with the new formatting requirements (Physicians Labeling Rule [PLR]) described in volume 71 of the Federal Register (January 24, 2006), pp. 3922 – 3997. The PLR should be submitted in both Word and PDF formats. We also refer to the November 8, 2006 telephone conversation between you and Ms. Jennifer Johnson of this Division in which you were notified of this requirement and you stated that you were already working with a contractor to provide labeling in the new format. Although we received the draft PLR through email on December 8, 2006, we remind you to officially submit a final PLR version as soon as possible.
3. We note that the structured product labeling (SPL) has not been submitted representing the content of your proposed labeling. You are required to submit prescribing information (i.e., the package insert) in SPL format by regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Content of Labeling* (April 2005); and <http://www.fda.gov/ohrms/dockets/92s0251/92s-0251-m000032-vol1.pdf>.] The content of labeling (SPL) must be submitted in extensible mark-up language (xml).

PHARMACEUTICAL SPECIALTIES...  
PROMOTED ETHICALLY



Mary Parks, M.D.

Re: \_\_\_\_\_ Nasal Spray

505(b)(2) New Drug Application No. 022-102

Serial No. 0001 – Labeling Amendment

Page 3 of 3

b(4)

If there are any questions concerning this submission, please contact Christina Patullo, Regulatory Affairs Manager, at the following address:

Fleming & Company, Pharmaceuticals  
1733 Gilsinn Lane  
Fenton, MO 63026

Telephone: (636) 343-5306 x 333  
Facsimile: (636) 343-5322  
E-mail: cpatullo@flemingcompany.com

Sincerely,



Phillip W. Dritsas  
President

Enclosures

cc: C. Patullo, Fleming & Company, Pharmaceuticals  
M. Whalon, Beckloff Associates, Inc.

APPEARS THIS WAY ON ORIGINAL

TO (Office/Division):  
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420, WO22, Rm 4447  
2) DSRCs

FROM (Name, Office/Division, and Phone Number of Requestor):  
Jennifer Johnson, Regulatory Project Manager, DMEP, HFD-510, WO22, Rm 3393, 301-796-2194

|                           |         |                   |  |  |
|---------------------------|---------|-------------------|--|--|
| DATE<br>December 13, 2006 | IND NO. | NDA NO.<br>22-102 | TYPE OF DOCUMENT<br>New Drug Application,<br>505(b)(2) | DATE OF DOCUMENT<br>September 26, 2006 |
|---------------------------|---------|-------------------|--|--|

|  |                                    |                                   |   |
|--|------------------------------------|-----------------------------------|---|
| NAME OF DRUG<br>Nasal Spray<br>(cyanocobalamin, USP),<br>25 mcg/0.1 ml | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>Vitamin | DESIRED COMPLETION DATE<br>May 25, 2007 |
|--|------------------------------------|-----------------------------------|---|

NAME OF FIRM: Fleming & Company, Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

1) DMETS: Please review trade name, package insert and carton and container labeling. This application is located in the EDR. The carton and container labeling was submitted on the original application date of September 26, as well as the package insert in the old format. The company has been notified of the new PLR formatting requirements, and plans on submitting this by December 18, 2006.

SRCS: Please review the patient instruction sheet included in the labeling.

UF Goal Date=July 27, 2007

|  |  |
|--|--|
| SIGNATURE OF REQUESTOR<br>Jennifer Johnson | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |
| PRINTED NAME AND SIGNATURE OF RECEIVER     | PRINTED NAME AND SIGNATURE OF DELIVERER  |

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/s/

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Jennifer Johnson  
12/13/2006 02:20:12 PM

**Johnson, Jennifer**

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From: cderdocadmin@cder.fda.gov  
Sent: Wednesday, December 13, 2006 2:35 PM  
To: Johnson, Jennifer  
Subject: DFS Email - N 022102 N 000 26-Sep-2006 - Forms

Attachments: 09001464806f88fe.drl; 09001464806f88fe.pdf



09001464806f88fe.09001464806f88fe.  
drl (170 B) pdf (22 KB)

Document room update the following:  
Decision Date Decision Code

N 022102 N 000 26-Sep-2006 13-Dec-2006 :

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Document Type: Forms  
Form Group: CONSULT  
Form Name: ODS Consult (Except Tradename Reviews)  
Submission Description: DSRCS\_Conult\_Request

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Author(s)/Discipline(s)

1. Jennifer Johnson, CSO

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Signer(s)

Jennifer Johnson  
13-Dec-2006

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Supervisory Signer(s)

1. Jennifer Johnson  
13-Dec-2006

APPEARS THIS WAY ON ORIGINAL

12/18/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-102

Fleming & Company, Pharmaceuticals  
Attention: Christina Patullo  
Regulatory Affairs Manager  
1733 Gilsinn Lane  
Fenton, MO 63026

Dear Ms. Patullo:

Please refer to your September 26, 2006, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for \_\_\_\_\_ Nasal Spray (Cyanocobalamin, USP), 25 mcg/0.1mL.

b(4)

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on December 10, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues, and we request that you submit the following information:

Clinical Pharmacology

1. Your application contained no summary for the analytical methods and validation, and the summary is a required section for the study report even if the analytical method is a commercially available kit. Therefore, please submit the summary information or tell us its location if it has been submitted.

Labeling

2. All new drug applications submitted on or after June 30, 2006, are required to include Prescribing Information (PI) that complies with the new formatting requirements (Physicians Labeling Rule [PLR]) described in volume 71 of the Federal Register (January 24, 2006), pp. 3922 – 3997. The PLR should be submitted in both Word and PDF formats. We also refer to the November 8, 2006, telephone conversation between you and Ms. Jennifer Johnson of this Division in which you were notified of this requirement and you stated that you were already working with a contractor to provide labeling in the new format. Although we received the draft PLR through email on December 8, 2006, we remind you to officially submit a final PLR version as soon as possible.

3. We note that structured product labeling (SPL) has not been submitted representing the content of your proposed labeling. You are required to submit prescribing information (i.e., the package insert) in SPL format by regulation [21 CFR 314.50(i), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); and <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf>.] The content of labeling (SPL) must be submitted in extensible mark-up language (*xml*).

During the initial implementation phase of the PLR until the end of 2006, FDA is advising applicants to make a good faith effort to provide PLR-compliant structured product labeling (SPL) with their marketing applications or efficacy supplements. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email [spl@fda.hhs.gov](mailto:spl@fda.hhs.gov) for individual assistance. Also, please submit evidence of your good faith effort to provide PLR-compliant SPL as soon as possible.

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 Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

*{See appended electronic signature page}*

Enid Galliers  
Chief, Project Management Staff  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/

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Enid Galliers

12/8/2006 06:29:22 PM

**Johnson, Jennifer**

---

**From:** Sahlroot, Jon T  
**Sent:** Friday, November 17, 2006 3:00 PM  
**To:** Lubas, William (CDER)  
**Cc:** Kehoe, Theresa; Johnson, Jennifer  
**Subject:** RE: \_\_\_\_\_ NDA (Oceans 12)

b(4)

Bill,

Here's what I emailed to Jennifer on October 20 --

*I do not think a stat review review will be necessary for this submission. As far as I can tell from the DFS record, statistics has not been involved with this drug at any time during its development. The clinical study that was submitted (PR99-063), while called a safety and "efficacy" study by the sponsor, is really a pharmacokinetic study. The data for this study is, in fact, included in the Pharmacokinetics section of the proposed label. The 510 statisticians as a rule don't evaluate the statistics of PK studies unless the designs or analyses are non-standard or unusual. We will of course be available for consult to Biopharm if they have questions about the data for this study.*

Regarding the proposed statement in the label...

that daily administration results in "slightly higher \_\_\_\_\_ than those seen 2 to 4 weeks after administration of IM B12".

b(4)

...I see that it doesn't contain p-values or statements of statistical significance. Are you looking to add statistical significance to this statement?

Todd

---

**From:** Lubas, William (CDER)  
**Sent:** Tuesday, November 14, 2006 2:26 PM  
**To:** Sahlroot, Jon T  
**Cc:** Kehoe, Theresa  
**Subject:** \_\_\_\_\_ NDA \_\_\_\_\_

b(4)

Hi Todd,

We had the filing meeting today for this once a day Vit B12 nasal spray.

I remember Japo was at the PreNDA meeting and we had discussed using descriptive stats to review the PD study in this NDA. Since that was the case, I guess you weren't invited to the meeting today.

In the submission the sponsor decided to try to do some statistics to analyze the data and did repeated measures estimates at 2, 4, 6 and 8 weeks after the last IM dose. The data was statistically significant if they looked at the ratio of B12 to baseline ( $p=0.0096$ ) or to the upper limit of normal ( $p=0.0001$ ) but not if they looked at absolute differences ( $p=0.063$  and  $p=0.059$  log transformed data).

The only reason this may become an issue is that they plan to say that daily administration results in "slightly higher \_\_\_\_\_ than those seen 2 to 4 weeks after administration of IM B12". I don't like this statement for several reasons but the current label for the innovator product Nascobal has even a stronger statement in the label "weekly nasal administration results in statistically higher serum Vit B12 levels than after intramuscular administration ." so I was wondering if it might be worth having a stats review of this single study anyway so that we would know what would be reasonable to put in the label. There is only one study with 25 patients so it shouldn't be a lot of work. This will be the first B12 to incorporate the new SPL label so it might be a good time

b(4)

to try to straighten out whether a relative efficacy statement such as this should be in the label.

Let us know what you think,

Thanks,  
Bill

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

TO (Office/Division):  
James McVey, Microbiology, 301-796-1572

FROM (Name, Office/Division, and Phone Number of Requestor):  
Jennifer Johnson, Project Manager, DMEP,  
301-796-2194

DATE  
November 13, 2006

IND NO.  
58,346

NDA NO.  
22-102

TYPE OF DOCUMENT  
New NDA

DATE OF DOCUMENT  
September 26, 2006

NAME OF DRUG  
Nasal Spray  
(Cyanocobalamin, USP)

PRIORITY CONSIDERATION  
S

CLASSIFICATION OF DRUG  
Vitamins other than D

DESIRED COMPLETION DATE  
TBD (PDUFA Goal  
Date=July 27, 2007; filing  
date=November 26, 2006) b(4)

NAME OF FIRM: Fleming and Company, Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology consult is requested for a review of the microbial limits and preservative effectiveness testing/results. The CMC reviewer is Su Tran, and she can be contacted at 301-796-1764. This is an electronic submission, located in the EDR under NDA 22-102. This is a 505(b)(2) application.

SIGNATURE OF REQUESTOR  
Jennifer Johnson

METHOD OF DELIVERY (Check one)  
 DFS  EMAIL  MAIL  HAND

PREPARED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

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Jennifer Johnson  
11/13/2006 02:08:13 PM

**Johnson, Jennifer**

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**From:** Sahlroot, Jon T  
**Sent:** Friday, October 20, 2006 10:49 AM  
**To:** Johnson, Jennifer  
**Subject:** RE: Reviewers for NDA 22-102/ ~~\_\_\_\_\_~~ Nasal Spray

b(4)

Jennifer,

I do not think a stat review review will be necessary for this submission. As far as I can tell from the DFS record, statistics has not been involved with this drug at any time during its development. The clinical study that was submitted (PR99-063), while called a safety and "efficacy" study by the sponsor, is really a pharmacokinetic study. The data for this study is, in fact, included in the Pharmacokinetics section of the proposed label. The 510 statisticians as a rule don't evaluate the statistics of PK studies unless the designs or analyses are non-standard or unusual. We will of course be available for consult to Biopharm if they have questions about the data for this study.

Thanks,.

todd

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**From:** Johnson, Jennifer  
**Sent:** Thursday, October 19, 2006 5:48 PM  
**To:** Davis Bruno, Karen L; Sahlroot, Jon T  
**Cc:** Lubas, William (CDER); Tran, Suong T; Chung, Sang  
**Subject:** Reviewers for NDA 22-102/ ~~\_\_\_\_\_~~ Nasal Spray

b(4)

Hello!

I just wanted to check in and see who the reviewers will be for this NDA that came in on September 29th (pharm/tox and stats; the definite reviewers are Cc'd on this email). I'll be scheduling the filing meeting shortly and would like to know who to invite.

Su, do you think that a CDRH consult will be needed? If so, what section(s) apply? How about a micro consult? I'll be doing consults for this NDA next week.

Thanks much!  
~Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research, FDA**  
**301-796-2194 phone**  
**301-796-9712 fax**  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

10/6/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-102

**NDA ACKNOWLEDGMENT**

Fleming & Company, Pharmaceuticals  
Attention: Christina Patullo  
Regulatory Affairs Manager  
1733 Gilsinn Lane  
Fenton, MO 63026

Dear Ms. Patullo:

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: \_\_\_\_\_ 'Nasal Spray (Cyanocobalamin, USP), 25 mcg/0.1 mL

b(4)

Review Priority Classification: Standard (S)

Date of Application: September 26, 2006

Date of Receipt: September 27, 2006

Our Reference Number: NDA 22-102

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 November 26, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 27, 2007.

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 requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. We will respond to this request during the review of the application.

NDA 22-102

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-2194.

Sincerely,

*{See appended electronic signature page}*

Jennifer Johnson  
Regulatory Project Manager  
Division of Metabolism and Endocrinology 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.**  
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/s/

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Jennifer Johnson  
10/6/2006 03:22:57 PM

**USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET**

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

A # 22-102 SUPP TYPE & # N-000 Division HFD-510 UFID # 3006720 b(4)

Applicant Name: Fleming's Company Pharmaceuticals Drug Name: Nasal Spray (Cyanocobalamin USP)

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?

Yes  No

2. Firm in Arrears?

Yes  No

3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees"

<http://www.fda.gov/cder/guidance>

Yes  No (explain in comments)

4. Administrative Split? (list all NDA#s and Divisions)

| NDA #/Doc Type | Div. | Fee? (Y/N) |
|----------------|------|------------|
|                |      |            |
|                |      |            |
|                |      |            |

5. Type 6?

Yes  No

Type 6 to which other application?

NDA # \_\_\_\_\_ Supp Type & # \_\_\_\_\_

6. Clinical Data Required for Approval? (Check one)

Yes\*

Yes, by reference to another application

NDA # \_\_\_\_\_ Supp Type & # \_\_\_\_\_

No

\* Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)" 25mg/0.1mL  
<http://www.fda.gov/cder/guidance>

Yes  No  To be determined

8. Subpart H (Accelerated Approval/Restricted Distribution)?

Yes  No  To be determined

9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)

List of exclusions:

- 2 - No fee - administrative split
- 4 - No fee - 505b2
- 7 - Supplement fee - administrative split
- 9 - No fee Subpart H supplement - confirmatory study
- 11 - No fee Orphan Exception
- 13 - No fee State/Federal exemption from fees

10. Waiver Granted?

Yes (letter enclosed)  No

Select Waiver Type below: Letter Date: \_\_\_\_\_

Small Business  Barrier-to-Innovation  
 Public Health  Other (explain)

11. If required, was the appropriate fee paid?

Yes  No

12. Application Review Priority

Priority  Standard  To be determined

13. Fast Track/Rolling Review Presubmission?

Yes  No

Comments

UFID = PD3006720

Jennif John 10/3/06  
PM Signature/Date

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

CC: original archival file  
HFD-007

Processor Name & Date

QC Name & Date

September 26, 2006

Mary Parks, M.D.  
Acting Director  
Division of Metabolism and Endocrinology Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Re: \_\_\_\_\_ <sup>t</sup>™ Nasal Spray (Cyanocobalamin, USP) b(4)  
505(b)(2) New Drug Application No. 022-102  
Original Submission

Dr. Parks:

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR 314.54, submitted herewith is an electronic 505(b)(2) NDA for \_\_\_\_\_ 'Nasal Spray (Cyanocobalamin, USP) (hereafter referred to as CobalaMist). b(4)

\_\_\_\_\_ is administered intranasally and is indicated for daily maintenance therapy for vitamin B<sub>12</sub> deficiency anemia following stabilization of plasma vitamin B<sub>12</sub> levels by intramuscular injections. b(4)

The reference listed drug upon which this application is based (see Module 1, Section 1.12.11) is Nascobal® (Cyanocobalamin, USP) Nasal Spray.

Fleming & Company, Pharmaceuticals (Fleming), submitted a pre-NDA meeting request and meeting package to Food and Drug Administration (FDA) on February 28, 2006, and April 11, 2006, respectively. FDA replied to the request with answers to the posed questions on May 11, 2006, in lieu of having a formal meeting. Correspondence relating to these interactions is provided in Section 1.6.1, Section 1.6.2, and Section 1.6.3. Correspondence from FDA on May 11, 2006, in the draft response to questions raised in the pre-NDA meeting package provides confirmation that it is acceptable that Fleming submit this application as a 505(b)(2) application. This correspondence is provided in Section 1.6.3.

Study No. PR99-063 was an open-label study to evaluate the safety and efficacy of \_\_\_\_\_ (referred to as OCEANS-12 vitamin B<sub>12</sub> nasal spray in the report) in 25 patients who previously required intramuscular vitamin B<sub>12</sub> injections to maintain normal serum B<sub>12</sub> levels. Patients replaced their maintenance B<sub>12</sub> injections with \_\_\_\_\_ once daily (daily dose 50 µg Cyanocobalamin) for 8 weeks. In this study, \_\_\_\_\_ effectively maintained therapeutic vitamin B<sub>12</sub> levels without significant safety issues. b(4)

PHARMACEUTICAL SPECIALTIES...  
PROMOTED ETHICALLY

Mary Parks, M.D.

Re: \_\_\_\_\_ Nasal Spray

505(b)(2) New Drug Application No. 022-102

Page 2

b(4)

Per 21 CFR 314.55(c)(2), Fleming requests a full waiver of the requirement that this application contain data to assess the use of \_\_\_\_\_ in the pediatric population. The request for a full waiver of the pediatric assessment is pursuant to 21 CFR 314.55(c)(2)(i) in that \_\_\_\_\_ does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

b(4)

As agreed by FDA in their response to the pre-NDA meeting package response (Section 1.6.3), 6 months of primary stability data is provided in this initial submission. Fleming commits to provide the 12-month data within 6 months of this submission date.

This electronic application consists of one volume containing the complete archival copy of the NDA submission (1 CD-ROM) and paper copies of the following documents containing original signatures: cover letter; Form FDA 356h; patent information (Form FDA 3542a); patent and debarment certifications; User Fee Cover Sheet (Form FDA 3397); financial disclosure (Form FDA 3454); exclusivity statement; and environmental analysis. Please note that documents containing original signatures are also provided in the electronic copy. Since this is an electronic submission, only one archival copy is provided.

In addition, this application is organized in Common Technical Document (CTD) format using the eCTD folder structure and replacing the XML backbone with PDF Tables of Contents. Minor variations from this format are incorporated as agreed by FDA in the response to the pre-NDA meeting package questions (Section 1.6.3).

Please note, a question regarding the requirements of Content and Format of Labeling for Human Prescription Drug Products and Structured Product Labeling (SPL) format were raised in the pre-NDA meeting package. FDA's response on May 11, 2006 (Section 1.6.3), stated that the draft labeling for CobalaMist in the current format would be acceptable by the Division at the time of filing of the 505(b)(2) application, with the understanding that the final labeling would be provided in the new SPL format (required as of June 30, 2006) prior to final approval of the marketing application.

The approximate size of the application is 220 MB. The CD-ROM has been scanned using the McAfee Virus Scan Enterprise 7.1 software, with a virus definition date of September 26, 2006, and were found to be virus free.

In addition, in accordance with 21 CFR 314.94 and the Guidance for Industry entitled *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, we request that the Electronic Document Room forward a copy of this submission to the Food and Drug Administration District Office in Lenexa, KS.

The user fee for this application was paid on September 6, 2006.

Mary Parks, M.D.

Re: \_\_\_\_\_ Nasal Spray

505(b)(2) New Drug Application No. 022-102

Page 3

b(4)

Please be advised that Fleming is committed to resolving any issues identified in the method validation process after approval.

If there are any questions concerning this submission, please contact Christina Patullo, Regulatory Affairs Manager, at the following address:

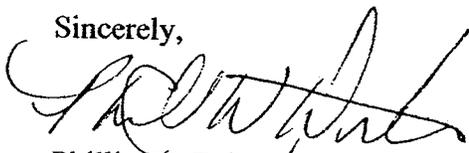
Fleming & Company, Pharmaceuticals  
1733 Gilsinn Lane  
Fenton, MO 63026

Telephone: (636) 343-5306 x 333

Facsimile: (636) 343-5322

E-mail: [cpatullo@flemingcompany.com](mailto:cpatullo@flemingcompany.com)

Sincerely,



Phillip W. Dritsas  
President

Enclosures

cc: C. Patullo, Fleming & Company, Pharmaceuticals  
A. Burnett, RRD Consulting  
J. DeLeon, Beckloff Associates, Inc.  
S. Pikulin, TechReg Services, Inc.

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG USER FEE  
COVERSHEET**

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>

|  |   |
|--|---|
| <p>1. APPLICANT'S NAME AND ADDRESS</p> <p>FLEMING AND COMPANY PHARMACEUTICALS<br/>Christina Patullo<br/>1733 Gilsinn Lane<br/>Fenton MO 63026<br/>US</p> | <p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>022-102</p>  |
| <p>2. TELEPHONE NUMBER</p> <p>636-343-5306 333</p>   | <p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>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:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p> |

|  |   |
|--|---|
| <p>3. PRODUCT NAME</p> <p>Nasal Spray ( Cyanocobalamin Nasal Spray )</p> | <p>6. USER FEE I.D. NUMBER</p> <p>PD3006720</p> |
|--|---|

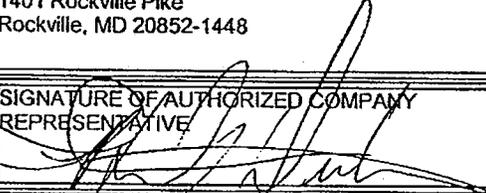
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

|   |  |
|---|--|
| <input type="checkbox"/> LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) | <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE   |
| <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act                    | <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY |

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

|  |  |  |
|--|--|--|
| Department of Health and Human Services<br>Food and Drug Administration<br>CBER, HFM-99<br>1401 Rockville Pike<br>Rockville, MD 20852-1448 | Food and Drug Administration<br>CDER, HFD-94<br>12420 Parklawn Drive, Room 3046<br>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. |
|--|--|--|

|  |                               |                               |
|--|-------------------------------|-------------------------------|
| <p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p>  | <p>TITLE</p> <p>President</p> | <p>DATE</p> <p>Sept. 6'06</p> |
|--|-------------------------------|-------------------------------|

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION  
\$767,400.00

Form FDA 3397 (12/03)

(IBE PRMT CLOSE G) (Print Cover sheet)

b(4)

**From:** Hedin, Durand M  
**Sent:** Thursday, May 11, 2006 3:25 PM  
**To:** 'patullo, chris'  
**Subject:** RE: IND#58,346

Hi Chris,

Attached are our draft answers to your questions. If you have any questions, contact me. If you are satisfied with the responses to your questions, and have no additional issues, please request that the meeting be cancelled.

Thanks,

Randy

*Randy Hedin, R.Ph.*

Commander, U.S. Public Health Service  
Senior Regulatory Management Officer  
U.S. Food and Drug Administration  
CDER, OND, ODE II, DMEP  
10903 New Hampshire Avenue  
Bldg. 22, Room 3344  
Silver Spring, MD 20993  
Phone: (301) 796-1224  
FAX: (301) 796-9712  
Email: durand.hedin@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

## Chemistry, Manufacturing, and Controls Questions

### 4.1.1 Drug Substance

1. Cyanocobalamin drug substance is manufactured by \_\_\_\_\_ as described in their respective Type II Drug Master File (DMF) and is tested for conformance to the current compendial (USP) requirements for release to Fleming. It is proposed that the specifications to be used by Fleming to release the \_\_\_\_\_ drug substance for commercial drug product manufacture will consist exclusively of the same USP monograph requirements, with full testing by Fleming for three drug substance batches and one batch at routine intervals thereafter, with certificate of analysis confirmation and minimal identification testing upon receipt for all other batches. Is this proposal acceptable to the Agency?

**Response:** *Yes, the proposal is acceptable provided that the drug substance specification be revised to add testing for impurities with limits established per ICH guidelines. Coordination between Fleming and \_\_\_\_\_ should be such that the drug substance specification implemented by both manufacturers includes the additional testing and acceptance criteria for impurities. Include the drug substance specification, batch analysis results from Fleming, and certificates of analysis from \_\_\_\_\_ in the NDA.*

### 4.1.2 Drug Product

1. Pursuant to 21 CFR 314.50(d)(1)(ii)(b-c) and 58 FR 47351, Fleming proposes to submit the following in the respective NDA drug product sections:
  - A detailed narrative manufacturing description in lieu of an unexecuted batch record;
  - An executed batch record for a single batch used in pivotal clinical studies;
  - An executed batch record for a single batch used in NDA stability studies.

Is this proposal acceptable to the Agency?

**Response:** *No, the proposal to submit in the NDA a detailed narrative manufacturing description in lieu of an unexecuted batch record is not acceptable. As required by 21 CFR 314.54 (a)(1)(i) and (2), the technical section described in 21 CFR 314.50(d)(1) is required to contain "the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product." The exception cited in 21 CFR 314.54 (a)(1)(i) and (2) does not allow the option in 21 CFR 314.50(d)(1) to provide "a comparably detailed description of the production process for a representative batch of the drug product." The executed batch*

*records for one batch used in the pivotal clinical studies and one batch used in the primary stability studies are acceptable in the NDA.*

2. As described in Section 7.0, Attachment 4, the clinical and proposed commercial drug product presentations differ slightly with regard to the pump assembly as follows:
- The diptube is slightly shorter for the proposed commercial presentation due to the somewhat smaller bottle size (1 oz for the proposed commercial presentation vs 55 cc nominal capacity for the clinical presentation).
  - The gasket material used for both the clinical and proposed commercial presentations consists of \_\_\_\_\_ with different suppliers used for each presentation, differing slightly \_\_\_\_\_ ratios.

b(4)

Other than these minor pump differences and the associated difference in bottle size, there are no differences in the formulations, container/closure materials, or the manufacturing processes.

On this basis, Fleming proposes to include the following information in the NDA to demonstrate comparability between the clinical and proposed commercial drug product presentations:

- Side-by-side comparison of all attributes of the clinical and proposed commercial drug product presentations as summarized above;
- Data demonstrating equivalency of the gaskets, including comparison of material characteristics, physiochemical data, and quantitative extractables profiles;
- Drug product release/stability data for both presentations, including spray pattern and droplet size distribution, to demonstrate comparable pump performance.
- Comparative data for selected drug product characterization studies for both presentations, including plume geometry, priming and tail off, to further demonstrate comparable pump performance.

Is this proposal acceptable to the Agency?

**Response:** *Yes, the proposal is acceptable.*

3. The following strategy is proposed with regard to preservative efficacy testing:
- The compendial antimicrobial preservative efficacy test (USP <51>) will be run on a developmental batch with the proposed marketed formulation/ packaging, and containing each of the preservative components (Benzyl Alcohol NF/Benzalkonium Chloride NF) at a concentration below the proposed lower specified shelf-life limits to demonstrate the robustness of the proposed specifications;

- USP <51> testing will be generated during the NDA stability program according to the protocol described in Section 7.0, Attachment 7;
- Assuming it is demonstrated that preservative efficacy is maintained in the above studies, the proposed marketed release/stability criteria for the preservative system will consist exclusively of assay testing for each preservative in lieu of USP <51> testing.

Is this proposal acceptable to the Agency?

**Response:** *Yes, the proposed studies are acceptable. The proposal to have assay testing for each preservative in lieu of USP <51> testing in the to-be-marketed product specification will be assessed as part of FDA's review of the preservative efficacy results from the described developmental batch study as well as from the described stability studies.*

4. The following plan is proposed for evaluation of leachables/extractables from the proposed marketed container/closure system:
  - Leachables data will be provided in the NDA for drug product stability batches.
  - A chromatographic extractables study will be performed for the elastomeric/plastic packaging components using solvents of varying properties.
  - In accordance with Section III.F.o of the July 2002 Guidance for Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products, a correlation will be established between the leachables and extractables data.
  - On the basis of this correlation, a commercial quality control packaging specification will be established for extractables in lieu of product leachables testing.

Does FDA agree with this approach?

**Response:** *Yes, the proposed studies are acceptable. The proposal to have extractables testing in lieu of leachables testing in the to-be-marketed product specification will be assessed as part of FDA's review of the extractables and leachables results from the described stability studies as well as the described correlation study.*

5. Fleming has obtained spray pattern and droplet size distribution data at both \_\_\_\_\_ and 6 cm distances and proposes to specify the \_\_\_\_\_ distance exclusively for both tests based on the comparability of data and demonstration from plume geometry data that the plume characteristics are similar at both distances with some diffusion observed at \_\_\_\_\_. With the understanding that acceptability is contingent upon review of the relevant data, is this proposal acceptable to the Agency?

b(4)

b(4)

**Response:** *Yes, the proposal is acceptable.*

6. Fleming is generating droplet size distribution data (by laser diffraction) for the droplet fraction \_\_\_\_\_ for multiple drug product batches. The available data indicate that about 2% of the droplets are consistently below \_\_\_\_\_. Pending completion of these analyses, Fleming proposes to omit the fraction \_\_\_\_\_ as part of the routine droplet size distribution specification. With the understanding that the Agency decision on this issue will ultimately be based on review of the data, is this strategy acceptable?

b(4)

**Response:** *Yes, the strategy is acceptable. The proposal to omit the fraction \_\_\_\_\_ as part of the droplet size distribution testing in the to-be-marketed product specification will be assessed as part of FDA's review of the described results.*

b(4)

7. Fleming proposes to submit 6 months of ICH long term and accelerated stability data for three batches of the proposed commercial drug product presentation as per the ongoing stability protocol provided in Section 7.0, Attachment 7, based on the following:
- In addition to the above stability data for the proposed commercial drug product presentation, up to 75 months of acceptable long term stability data will be provided in the NDA for two batches of the pivotal clinical drug product presentation, which differs only slightly from the proposed commercial drug product presentation as described in Question 2 (see Section 7.0, Attachments 4 and 6).
  - The expiration dating periods for similar commercial formulations containing cyanocobalamin (i.e., Nascobal<sup>®</sup> Nasal Spray; NDA 21-642; approved January 31, 2005 and Nascobal<sup>®</sup> Gel for Intranasal Administration; NDA 19-722; approved November 5, 1996) support the long term stability of the subject Fleming product.
  - The stability and forced degradation of cyanocobalamin in aqueous media have been extensively studied and are well-understood. Detailed discussion will be provided in the NDA, Fleming will be prepared to discuss these data in detail during the pre-NDA meeting if requested, and this information is being used along with stability/forced degradation data generated by Fleming to characterize and control the degradation profile.
  - All other information required for the NDA will be provided in the initial submission with the 6 month proposed commercial stability data. Since Fleming believes that 6 months of stability data at the time of initial NDA submission are adequate based on the rationale provided above, this proposal is in conformance with the Good Regulatory Management Practices (GRMP) guidance which calls for a complete application at the time of original NDA submission.

Does FDA agree with this approach?

**Response:** *Yes, the proposal to submit 6-month primary stability data in the initial submission of the NDA for filing is acceptable provided that an amendment be submitted within 6 months of the NDA initial submission to provide at minimum a total of 12-month long term primary stability data.*

#### 4.1.3 Miscellaneous

1. Other than the previously listed questions, are there any other issues regarding the information submitted in this package (e.g., specifications, proposed characterization studies, stability protocol, etc.)?

Response:

- *Add the following to the composition table of the drug product: amount of each component in mg/mL, and amount of each component per bottle to include the overfill.*
- *Provide a justification for the target amount of 12 g to be the overfill of formulation per bottle.*
- *The proposed "Simulated Patient Use Study" should include in-use stability testing of the product (same specification as in the proposed stability protocol including leachables testing, with both upright and horizontal storage orientations). If the in-use stability profile differs from the long-term stability profile, an in-use expiry would be required on labeling (e.g., "Use within ... weeks/months of first dosing") in addition to the long term storage expiry.*

#### 4.2 Nonclinical Questions

1. In the teleconference meeting minutes from March 16, 1999, FDA stated that "reference to the Nascobal preclinical studies as well as literature information on the vitamin B<sub>12</sub> vehicle will be sufficient for filing the NDA." Therefore, no additional preclinical studies were conducted for inclusion in the 505(b)(2) application, nor will any literature summaries regarding pharmacology or toxicology information on vitamin B<sub>12</sub> be included. As per the meeting minutes, reference will be made to the Nascobal<sup>®</sup> animal nasal mucosa irritation studies, and literature information on each of the \_\_\_\_\_ excipients will be included in the NDA. Does FDA agree with this approach?

**Response:** *Yes, we agree with this approach.*

b(4)

### 4.3 Clinical Questions

1. The proposed labeling is provided in Section 6.0. Do you agree that the clinical data presented are sufficient to support the proposed indication and are acceptable to FDA?

**Response:** The clinical data support the proposed indication. The acceptability of the data is a review issue.

2. Fleming plans to submit full data listings for all patients organized by case report form (CRF) type in the NDA. Fleming also intends to submit all CRFs and all Data Correction Forms (DCFs). Because the NDA will include just one clinical trial, Fleming believes that these data are sufficient to support the 505(b)(2) application and would like to request a waiver for patient case report tabulations. Does the FDA agree that a waiver is justified?

**Response:** *The data from the single clinical trial should include tabular safety and efficacy summaries.*

3. As part of the application review for \_\_\_\_\_ Spray for Intranasal Administration, we understand that per 21 CFR 314.55 (Pediatric use information), a pediatric assessment will need to be performed to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations. We propose to request a full waiver of pediatric requirements because Fleming is filing a 505(b)(2) application for \_\_\_\_\_ The \_\_\_\_\_ 505(b)(2) submission will reference the Nascobal<sup>®</sup> nasal spray prescribing information, which includes the following pediatric use indication: "Intake in pediatric patients should be in the amount recommended by the Food and Nutrition Board, National Academy of Science-National Research Council. (Refer to attached Dietary Reference Intakes Tables: Vitamins Table in Appendix 11.2)." We request guidance from the Division on whether \_\_\_\_\_ Spray for Intranasal Administration would qualify for a waiver and when the formal request should be submitted for review.

b(4)

b(4)

b(4)

**Response:** *A formal request can be submitted at any time. We recommend that you include a justification for why a study in pediatric patients would not be feasible.*

#### 4.4 Format Questions

1. In IND submission Serial 004 (18 March 2004), a general strategy for the \_\_\_\_\_ marketing application was presented by CTD Module, which included a detailed table of contents for Module 2. The application will follow the CTD format with regard to section and subsection designations as delineated in the ICH M4 guidance with exceptions as indicated in this pre-NDA briefing package in Section 5.0. Is the table of contents as outlined in Section 5.0 acceptable to the Agency? b(4)

**Response:** *Yes, the proposal is acceptable.*

2. The 505(b)(2) application will be provided in an electronic format generally consistent with the Agency guidance "Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications." Due to the normal differences between presentation of information in a 505(b)(1) versus 505(b)(2) application, along with consideration of sections not explicitly included in the ICH M4 guidances (e.g., drug product characterization studies), and to facilitate review, it is proposed that the submission will be provided as an eNDA. Is this proposal acceptable to the Agency?

**Response:** *Yes, the proposal is acceptable.*

3. In a telephone conference call held with Ms. Enid M. Galliers, Chief Project Manager, Division of Metabolic and Endocrine Products, CDER (February 6, 2006), the requirements regarding Content and Format of Labeling for Human Prescription Drug Products and Structured Product Labeling (SPL) format were discussed. From the outcome of that teleconference, it was determined that the draft labeling for \_\_\_\_\_ in the current format would be acceptable by the Division at the time of filing of the 505(b)(2) application, with the understanding that the final labeling would be provided in new SPL (required as of June 30, 2006) prior to final approval of the marketing application. Does the Division agree with this proposal for providing the draft labeling in the current format for the initial filing of the 505(b)(2) application? b(4)

**Response:** *Yes, we agree with the proposal.*

#### 4.5 Administrative Questions

1. Fleming believes that a user fee is not applicable to this 505(b)(2) application (see rationale below). Does the Agency consider Fleming's 505(b)(2) application to be a "human drug application," as defined in Food, Drug, and Cosmetic (FDC) Act § 735(1), for purposes of assessing Prescription Drug User Fee Act (PDUFA) user fees?

**Response:** *Please contact Mike Jones in the Office of Regulatory Policy at 301-443-5151 for all question regarding PDUFA user fees.*

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