

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-102**

**CHEMISTRY REVIEW(S)**

b(4)

(cyanocobalamin, USP)  
Nasal Spray  
25 mcg/spray

NDA 22-102

Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls

**Applicant:** Fleming & Company, Pharmaceuticals  
1733 Gilsinn Lane  
Fenton, MO 63026

**Indication:** \_\_\_\_\_

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**Presentation:** Each 100 microliter spray of the \_\_\_\_\_ Nasal Spray delivers 25 mcg of cyanocobalamin, USP.

Each presentation consists of a 30-mL plastic \_\_\_\_\_ fill bottle, fitted with a manual metered pump spray unit. The nasal spray pump is affixed to the fill bottle at the time of manufacture. Each bottle provides 30 doses and has a net fill weight of NLT 18.0 grams.

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**EER Status:** Acceptable 29-MAR-2007

**Consults:** Clin. Pharm: Acceptable 21-JUN-2007  
Pharm/Tox: Acceptable 7-JUN-2007  
EA: Categorical exclusion granted under 21 CFR §25.31 (a) (b) (c)  
Microbiology: Acceptable 5-DEC-2006  
Methods Validation: Method validation package is provided.  
Re-validation by the Agency is not needed at this time.

**Original Submission:** 26-SEPT-2006

**Drug Substance**

Cyanocobalamin, a synthetic form of vitamin B<sub>12</sub> with equivalent vitamin B<sub>12</sub> activity, has the chemical name α-(5,6-Dimethylbenzimidazolyl)cyanocobamide. It appears as an odorless and tasteless dark red crystal or crystalline powder with a molecular weight of 1355.4 g/mol and the molecular formula of C<sub>63</sub>H<sub>88</sub>CoN<sub>14</sub>O<sub>14</sub>P. Cyanocobalamin is the most stable and widely used form of vitamin B<sub>12</sub>.

Cyanocobalamin is very hygroscopic in its anhydrous form, and sparingly to moderately soluble in water. The pharmacologic activity of cyanocobalamin is destroyed by heavy metals (iron) and strong oxidizing or reducing agents (vitamin C), but not by autoclaving for a short period of time (15-20 min) at 121°C. The vitamin B<sub>12</sub> coenzymes are very unstable in light.

All information with respect to the chemistry and manufacturing controls of the drug substance cyanocobalamin, USP is provided by reference in DMF \_\_\_\_\_ (DMF holder : \_\_\_\_\_)

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\_\_\_\_\_ In addition to the USP monograph requirements, the drug substance is tested for impurities in accordance with ICH Q3A(R) guideline using the methodology described in the current European Pharmacopoeia monograph.

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A retest period of \_\_\_\_\_ for \_\_\_\_\_ and of \_\_\_\_\_ for description, structurally related impurities and assay were requested and are approved, when stored at the drug product manufacturing facility (Fleming) at room temperature in aluminum cans with \_\_\_\_\_ seals. The proposed retest periods are supported by the stability data (shelf-life) provided in DMF \_\_\_\_\_

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**Conclusion:** Drug substance is acceptable.

#### **Drug Product**

\_\_\_\_\_ Nasal Spray is a metered-dose, manual-pump spray assembly containing an isotonic, non-sterile, aqueous solution of cyanocobalamin, USP (vitamin B<sub>12</sub>) that delivers 25 mcg per actuation. The drug product is a clear, red to light red, aqueous solution contained in a plastic \_\_\_\_\_ bottle and is available as a 60 puff/bottle presentation.

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Each bottle of \_\_\_\_\_ Nasal Spray contains \_\_\_\_\_ cyanocobalamin, USP, \_\_\_\_\_ sodium chloride, USP; \_\_\_\_\_ monobasic sodium phosphate, \_\_\_\_\_, USP; \_\_\_\_\_; benzyl alcohol, NF; \_\_\_\_\_ benzalkonium chloride, \_\_\_\_\_ NF; \_\_\_\_\_ sodium hydroxide, NF; and \_\_\_\_\_ Purified Water, USP. Each bottle of \_\_\_\_\_ Nasal Spray is filled with NLT 18 mL of the formulation and is intended to deliver 60 sprays (100 µl per actuation) each of 25 mcg cyanocobalamin, USP. A daily dose of \_\_\_\_\_ Nasal Spray of 50 µg is administered in two (2) sprays (one in each nostril). Each bottle provides 30 doses and has a net fill weight of NLT 18.0 grams.

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The proposed release specifications include appearance (formulation), appearance (container/closure system), identity by HPLC, identity by UV spectroscopy, pH, osmolarity, viscosity, net content, assay by HPLC, drug-related impurities by HPLC, preservative content (benzyl alcohol, benzalkonium chloride) by HPLC, pump delivery, spray content uniformity, spray pattern, droplet size distribution by laser imaging/ diffraction, particulate matter by microscopy, microbial limits, and leachables. The proposed regulatory methods have been validated.

Adequate stability data were provided to support the requested expiration dating period of 24 months for the drug product, stored upright with cap in place, at controlled room temperature of 25°C (77°F) with excursions permitted between 15° and 30 °C (59° and 86°C). Drug product should NOT be stored in the refrigerator or freezer.

**Conclusion:** Drug product is satisfactory.

#### **Additional Items:**

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

A method validation package, describing the test methods and validation procedures, including information supporting the reference standard, is provided. Re-validation of any of the specific test methods by the field laboratories is not needed at this time.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for **Approval**, pending agreement on product labeling.

Blair A. Fraser, Ph.D.  
Director  
DPA I/ONDQA

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# Chemistry Review Data Sheet

- 1. NDA #: 22-102
- 2. REVIEW #: # 1
- 3. REVIEW DATE: Jul-01-2007
- 4. REVIEWER: Yvonne Yang, Ph.D.
- 5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original  
 Labeling information and proposal of alternative names  
 Minor Chemistry amendment (stability data)  
 Minor Chemistry amendment (Table 3.2.P.1-1)

Sept-26-2006  
 Jan-22-2007  
 Mar-15-2007  
 Jun-21-2007

7. NAME & ADDRESS OF APPLICANT:

**Name:** Fleming & Company, Pharmaceuticals  
**Address:** 1733 Gilsinn Lane, Fenton, MO 63026  
**Representative:** Philip W. Dritsas, President  
**Telephone:** 636-343-5306, x333

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Cyanocobalamin
- c) Code Name/# (ONDQA only): CAS-68-19-9
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5
  - Submission Priority: S

b(4)

9. LEGAL BASIS FOR SUBMISSION:

This NDA is submitted as a 505(b)(2) application.



# CHEMISTRY REVIEW



## Chemistry Assessment Section

10. PHARMACOL. CATEGORY: Vitamins other than D
11. DOSAGE FORM: Spray, Metered
12. STRENGTH/POTENCY: 25 mcg/0.1 mL/actuation
13. ROUTE OF ADMINISTRATION: Intranasal
14. Rx/OTC DISPENSED:     X     Rx      OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

     SPOTS product – Form Completed

  X   Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cyanocobalamin, USP (vitamin B<sub>12</sub>)

C<sub>63</sub>H<sub>88</sub>CoN<sub>14</sub>O<sub>14</sub>P (MW = 1355.4 Dalton) (see review for structural formula)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF | TYPE | HOLDER | ITEM REFERENCED     | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS            |
|-----|------|--------|---------------------|-------------------|---------------------|-----------------------|---------------------|
|     | II   |        | Cyanocobalamin, USP | 1                 | Adequate            | Jun-15-2007           | Reviewed By Y. Yang |
|     | III  |        |                     | 4                 | N/A                 | N/A                   | N/A                 |
|     | III  |        |                     | 1                 | Adequate            | Jun-20-2007           | Reviewed By Y. Yang |
|     | III  |        |                     | 1                 | Adequate            | Jun-21-2006           | Reviewed By Y. Yang |
|     | III  |        |                     | N/A               | N/A                 | N/A                   |                     |
|     | III  |        |                     | N/A               | N/A                 | N/A                   |                     |
|     | III  |        |                     | N/A               | N/A                 | N/A                   |                     |

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<sup>1</sup> Action codes for DMF Table:  
1 – DMF Reviewed.



# CHEMISTRY REVIEW



## Chemistry Assessment Section

Other codes indicate why the DMF was not reviewed, as follows:

- 2 - Type 1 DMF
- 3 - Reviewed previously and no revision since last review
- 4 - Sufficient information in application
- 5 - Authority to reference not granted
- 6 - DMF not available
- 7 - Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION                                  |
|----------|--------------------|--|
| IND      | 58,346             | Pre-NDA CMC correspondence dated May-11-2006 |

### 18. STATUS:

#### ONDQA:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION  | DATE                               | REVIEWER          |
|-------------------------------|---|------------------------------------|-------------------|
| Methods Validation            | Acceptable  |                                    | Yvonne Yang       |
| EA                            | Categorical exclusion granted   |                                    | Yvonne Yang       |
| EES                           | Acceptable overall recommendation from OC                                 | Mar-29-2007                        |                   |
| Microbiology                  | Approval from microbiology product quality standpoint                     | Dec-05-2006<br>(signed off in DFS) | Vinayak Pawar     |
| Pharm/Tox                     | Approval  | Jun-07-2007<br>(signed off in DFS) | Karen Davis-Bruno |
| Biopharm                      | Acceptable  | Jun-21-2007<br>(signed off in DFS) | Sang Chung        |
| OSE/DMETS                     | Pending   |                                    |                   |
| ODS/DSRCS                     | Recommendation and comments for revision of the Patient Instruction Sheet | May-25-2007<br>(signed off in DFS) | Jeanine Best      |



# The Chemistry Review for NDA 22-102

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 22-1022 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls pending final labeling including Tradename.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Product:

Cyanocobalamin is currently available on the US market, under prescription, in the dosage forms of both injection and metered spray (nasal spray). The proposed drug product, : \_\_\_\_\_ <sup>4</sup> Nasal Spray, is supplied as a multi-dose, non-sterile isotonic aqueous solution containing cyanocobalamin, USP (vitamin B<sub>12</sub>) for administration as a metered spray to the nasal mucosa (an intranasal spray). Each carton of the drug product contains one 30-ml plastic \_\_\_\_\_ fill bottle and one nasal spray pump ( \_\_\_\_\_ 100 µL metered pump/screw top closure), a package insert, and a patient instruction sheet. The nasal spray pump is affixed to the fill bottle at the time of manufacture. Each bottle of \_\_\_\_\_ <sup>4</sup> Nasal Spray contains cyanocobalamin, USP, sodium chloride, USP; monobasic sodium phosphate, \_\_\_\_\_ USP; benzyl alcohol, NF; \_\_\_\_\_ benzalkonium chloride, \_\_\_\_\_ NF; \_\_\_\_\_ sodium hydroxide, NF; and Purified Water, USP. Each bottle of \_\_\_\_\_ <sup>4</sup> Nasal Spray is filled with 18 mL of the formulation, and intended to deliver 60 sprays (100 µl per actuation), and each spray 25 µg cyanocobalamin, USP. A daily dose of \_\_\_\_\_ Nasal Spray of 50 µg is administered in two (2) sprays (one in each nostril). Each bottle of \_\_\_\_\_ Nasal Spray will deliver 30 doses.

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The drug product has been extensively characterized and tested in general accordance with the requirements provided in the July 2002 FDA guidance *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation*.



# CHEMISTRY REVIEW



## Chemistry Assessment Section

ingestion of hot foods or liquids. Periodic monitoring of serum B<sub>12</sub> levels should be done to establish adequacy of therapy.

### C. Basis for Approvability or Not-Approval Recommendation

NDA 22-102 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls, pending final labeling including Tradename.

CMC information provided to support the application includes the following:

- Adequate CMC information for the drug substance cyanocobalamin, USP (DMF \_\_\_\_\_)
- Adequate CMC information for the drug product \_\_\_\_\_ ' Nasal Spray
- Acceptable regulatory specification for the drug substance cyanocobalamin, USP
- Acceptable regulatory specification for the drug product \_\_\_\_\_ " Nasal Spray
- Sufficient stability data to support the proposed expiration dating period for \_\_\_\_\_ ' Nasal Spray (24 months when stored at controlled room temperature [15-30 °C or 59-86 °F] protected from light).
- Adequate CMC information for container closure system (DMF \_\_\_\_\_, DMF \_\_\_\_\_)
- Approval recommendation from Microbiology product quality standpoint
- Overall cGMP status was found acceptable by Office of Compliance for all manufacturing and testing facilities.

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### III. Administrative:

- A. Reviewer's Signature in DFS
- B. Endorsement Block: in DFS
- C. CC Block: in DFS

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✓ Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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Blair Fraser  
7/2/2007 12:47:07 PM  
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## Initial Quality Assessment

### OND Division of Metabolism and Endocrinology Products

NDA: 22-102

Applicant: Fleming & Company, Pharmaceuticals

Stamp Date: 27-SEP-2006

PDUFA Date: 27-JUL-2007

Proposed Proprietary Name: \_\_\_\_\_

Established Name: cyanocobalamin

Dosage form and strength: 25 mcg per 0.1 mL nasal spray (50 mcg daily dose)

Route of Administration: intranasal

Indications: Daily maintenance therapy for vitamin B12 deficiency \_\_\_\_\_

PAL: Su (Suong) Tran, Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer

#### Time goals:

- IQA/Chemistry filing memo in DFS: by 4-NOV-2006
- Filing decision "Day 45": 4-NOV-2006 (tentative; to be set by Clinical Division)
- Filing review issues "Day 74": 10-DEC-2006 (tentative; to be set by Clinical Division)
- Chemistry Review (DR/IR) letter: by 27-FEB-2007
- Mid-cycle meeting "Month 5": 27-FEB-2007 (tentative; to be set by Clinical Division)
- Final Chemistry Review "Month 8" in DFS: by 27-MAY-2007
- PDUFA: 27-JUL-2007

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# Initial Quality Assessment

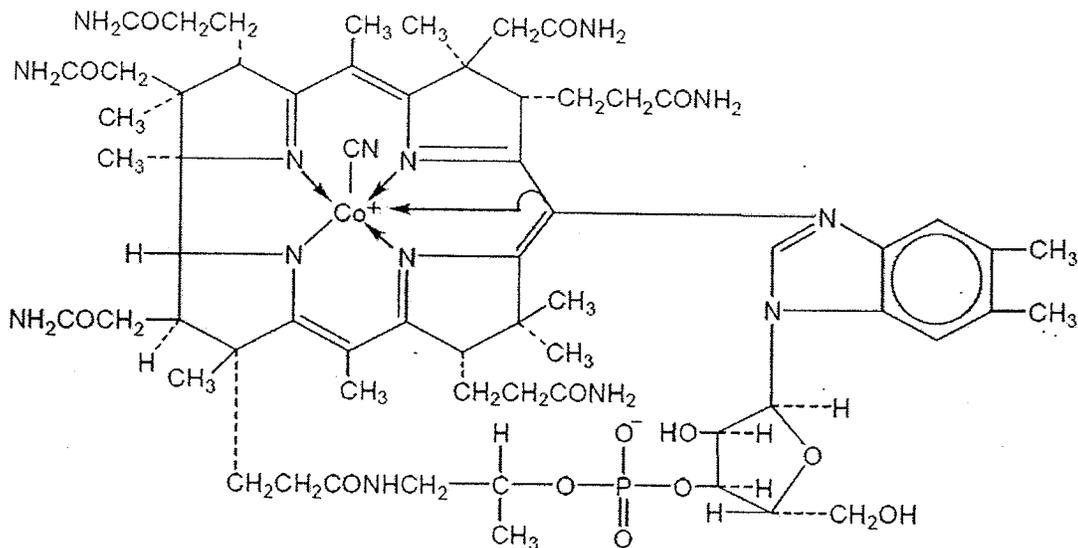
| CONSULTS/ CMC RELATED REVIEWS | COMMENT  |
|-------------------------------|--|
| Biopharm/ClinPharm            | <i>May not be applicable</i>   |
| CDRH                          | <i>May not be applicable</i>   |
| EA                            | Categorical exclusion request to be assessed by Primary Reviewer   |
| EES                           | EER sent to Office of Compliance on 19-OCT-2006  |
| DMETS                         | <i>Labeling consult request will be sent as part of DMEP's request.</i>  |
| Methods Validation            | To be assessed by Primary Reviewer   |
| Microbiology                  | Consult request will be sent by the PM for the evaluation of microbial limits and preservative effectiveness test/results. |
| Pharm/Tox                     | Consult may be needed to assess the limits on extractables, nonvolatile residue, and particulate matter.                   |

### Summary:

- This is an electronic NDA, filed as a 505(b)(2) application. The associated IND is IND 58346.
- The clinical proof of this NDA consists of one Phase 3 efficacy study (Study PR99-063) using drug product Batches 9036 and 0060116. Commercial registration batches are 0500314, 0500318, and 0500326.
- The drug substance is cyanocobalamin, USP. Reference is made to the DMF — (DMF holder: \_\_\_\_\_) for all chemistry information on the drug substance.

USAN: cyanocobalamin

Chemical name: Vitamin B12 (per 2006 USP Dictionary)



Molecular formula:  $C_{63}H_{88}CoN_{14}O_{14}P$

Molecular weight: 1355.4

# Initial Quality Assessment

- Drug product:

The drug product is a nasal spray, formulated as a multi-dose, non-sterile isotonic aqueous solution in a \_\_\_\_\_ bottle, filled to contain NLT 18 mL (or 18 g) per bottle, with an attached 100 microL metered pump/screw top closure. Excipients are: sodium chloride USP, monobasic sodium phosphate \_\_\_\_\_ USP, benzyl alcohol NF, sodium hydroxide NF, benzalkonium chloride \_\_\_\_\_ NF, and purified water USP. The drug product will be administered as a 25 mcg cyanocobalamin per actuation per nostril to provide a dose of 50 mcg (once a day).

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**Table 2.3.P.1-1. Drug Product Unit Composition**

| Ingredient                            | Amount                |         |         |                        |                      | Function          |
|---------------------------------------|-----------------------|---------|---------|------------------------|----------------------|-------------------|
|                                       | µg/spray <sup>a</sup> | mg/mL   | wt %    | mg/bottle <sup>b</sup> |                      |                   |
|                                       |                       |         |         | 60 sprays              | 60 sprays + overfill |                   |
| <b>Drug Substance:</b>                |                       |         |         |                        |                      |                   |
| Cyanocobalamin, USP                   | 25                    | 0.25    | 0.025   | 1.5                    | 4.5                  | Active ingredient |
| <b>Excipients:</b>                    |                       |         |         |                        |                      |                   |
| Sodium Chloride, USP                  |                       |         |         |                        |                      |                   |
| Monobasic Sodium Phosphate, _____ USP |                       |         |         |                        |                      |                   |
| Benzyl Alcohol, NF                    |                       |         |         |                        |                      |                   |
| Sodium Hydroxide, NF                  |                       |         |         |                        |                      |                   |
| Benzalkonium Chloride, _____ NF       |                       |         |         |                        |                      |                   |
| Purified Water, USP                   |                       |         |         |                        |                      |                   |
| <b>Total</b>                          | 100 mg                | 1000.00 | 100.000 | 6000                   | 18000                |                   |

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<sup>a</sup> Based on a nominal spray of 100 µL (=100 mg) per actuation.

<sup>b</sup> The stated values are based on 60 sprays = 6 g with an overfill to give a total content of NLT 18 g/bottle.

- Stability: The NDA includes 6-month stability for 3 primary stability batches stored at 25 °C/60% RH and 40 °C/75% RH, packaged in the commercial container closure system and manufactured at or near full commercial scale. Per pre-NDA agreement, a total of 12-month data will be provided to the NDA within 6 months of the initial submission.
- Packaging system: There is one primary container closure system consisting of an \_\_\_\_\_ bottle (to contain 18 mL of drug formulation) and an attached 100 microL metered pump/screw top closure. The components are copied below. The primary container closure is packaged in a carton.

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# Initial Quality Assessment

**Table 2.3.P.7-1. Overview of Container Closure System Components**

| Component | Subcomponent | Material(s) of Construction | Regulatory Citation(s) | Supplier |
|-----------|--------------|-----------------------------|------------------------|----------|
|           |              | See below                   | Type III DMF Nos.      |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | ----                   |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1350       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §181.28         |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | Type III DMF No.       |          |
|           |              |                             | Type III DMF No.       |          |
|           |              |                             | 21 CFR §177.1520       |          |
|           |              |                             | Type III DMF No.       |          |
|           |              |                             | 21 CFR §177.1520       |          |

- Relevant product batches:

|         |  |
|---------|--|
| 0060116 | Phase 3 efficacy study (Study PR99-063)<br>Product characterization study: priming/repriming in different orientations, plume geometry   |
| 9036    | Phase 3 efficacy study (Study PR99-063)<br>Product characterization study: profiling of sprays near container exhaustion, plume geometry   |
| 0500314 | Primary stability<br>Product characterization study: temperature cycling, priming/repriming in different orientations, profiling of sprays near container exhaustion, particulate matter, plume geometry, and fill weight and dip tube length                                |
| 0500318 | Primary stability<br>Product characterization study: simulated patient use, priming/repriming in different orientations, cleaning, device robustness, profiling of sprays near container exhaustion, particulate matter, plume geometry, and fill weight and dip tube length |
| 0500326 | Primary stability<br>Product characterization study: photostability, plume geometry  |

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## Initial Quality Assessment

### CRITICAL ISSUES (this is not an exhaustive list of critical issues. See Chemistry Review by Primary Reviewer for additional critical issues):

- Has all information requested during the IND phases, and at the pre-NDA meetings been included?  
YES

Pre-NDA chemistry comments were conveyed to the sponsor on 11-MAY-2006 and 17-MAY-2006, in response to questions in the 11-APR-2006 briefing package. Fleming adequately documents the communication in the NDA and provides links to the requested information.

Several of the issues are discussed below as critical issues:

1. The drug substance is release-tested by the DMF manufacturer \_\_\_\_\_ per USP monograph requirements. The drug product manufacturer Fleming performs full testing per this same specification with the additional impurity testing and limits established per ICH guidelines on 3 drug substance batches and one batch at routine intervals thereafter, with certificate of analysis confirmation and identity testing upon batch receipt. The NDA includes the drug substance specification, batch analysis results from Fleming and certificates of analysis from \_\_\_\_\_.

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PAL's comment: The drug substance manufacturer \_\_\_\_\_ (and DMF holder) currently does not test for impurities in the drug substance because the USP monograph does not include this requirement. The applicant's (Fleming) drug substance specification in the NDA includes testing for impurities. The applicant's commitment "to perform testing for individual and total impurities as per specification on every batch received from the manufacturer \_\_\_\_\_ until such time that \_\_\_\_\_ incorporates the Fleming specification" is acceptable. This issue does not need to be pursued further because the applicant's proposed testing is an additional quality control to the compendial requirements that are adequate for several approved products.

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2. The NDA includes the master batch records and executed batch records for one batch used in the pivotal clinical studies and one batch used in the primary stability studies. [*Pre-NDA agreement; not a critical issue.*]
3. The NDA includes comparative results to link the clinical product to the commercial product, which differ in the length of the diptube, bottle size, and gasket material. Results are from these studies:
  - Side-by-side comparison of all attributes of the clinical and proposed commercial drug product presentations;
  - 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.

PAL's comment: The primary reviewer will evaluate the adequacy of the linkage between the clinical product and the commercial product.

4. Regarding the preservative effectiveness testing, results are provided as follows:

## Initial Quality Assessment

- The compendial antimicrobial preservative efficacy test (USP <51>) performed on a developmental batch with the proposed marketed formulation/ packaging, and containing each of the \_\_\_\_\_ 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 was used during the NDA stability program;

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PAL's comment: The Microbiology consult reviewer will evaluate the Microbial Limits and the antimicrobial preservative efficacy results. If the preservative effectiveness is found adequate by the Microbiology reviewer and is maintained during the stability studies, the applicant's proposal to have the release/stability criteria for the preservative system consisting of assay testing for each preservative in lieu of USP <51> testing would be acceptable.

5. Regarding the extractables/leachables testing of the packaging system, results are provided as follows in support of the proposal that "a commercial quality control packaging specification will be established for extractables in lieu of product leachables testing":
  - Leachables data on drug product stability batches;
  - Extractables data on the elastomeric/plastic packaging components using solvents of varying properties;
  - Correlation made between the leachables and extractables data.

PAL's comments: The primary reviewer will evaluate the adequacy of the correlation between the leachables in the drug product formulation and extractables profiles of the packaging components, and determine whether leachables testing is not necessary in the commercial stability specification.

- In addition, the reviewer will assess the following issue: There is no extractable in the specification even though the results show extractables in the bottle profiles using \_\_\_\_\_  
\_\_\_\_\_, Fleming will "perform routine \_\_\_\_\_ testing of the bottle as per USP <661> in lieu of \_\_\_\_\_ methodology." The proposed bottle specification includes limits on nonvolatile residue.
- The reviewer may obtain a Pharm.Tox. consult on the proposed limits on extractables, nonvolatile residue, and particulate matter.
- Note: Fleming commits to "perform full testing according to the pump specifications for the first 3 lots of commercial pumps [including extractables testing], and then will confirm the results for subsequent pump lots on a skip basis at periodic intervals". If the reviewer finds the extractables/leachables correlation to be adequate, this proposal would be acceptable.

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6. Spray pattern and droplet size distribution data are provided at both \_\_\_\_\_ and \_\_\_\_\_ distances. The applicant 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 \_\_\_\_\_ [Pre-NDA agreement; not a critical issue.]
7. Droplet size distribution data ( \_\_\_\_\_ ) for the droplet fraction \_\_\_\_\_ for multiple drug product batches. Fleming proposes to omit the fraction \_\_\_\_\_  $\mu\text{m}$  as part of the routine droplet

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## Initial Quality Assessment

size distribution specification because available data indicate that about 2% of the droplets are consistently below \_\_\_\_\_.

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PAL's comment: The primary reviewer will determine whether the proposed criteria for droplet size distribution at Dv(10), Dv(50), Dv(90), and span will adequately control this attribute without a limit on the droplet fraction \_\_\_\_\_. At the filing meeting, the Clinical review team indicated that this droplet fraction \_\_\_\_\_ is not clinically important because the inhalation route is not primary.

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8. 6-month primary stability data in the initial submission of the NDA for filing with a commitment that an amendment will be submitted within 6 months of the NDA initial submission to provide at minimum a total of 12-month long term primary stability data. *[Pre-NDA agreement; not a critical issue.]*
9. The composition table of the drug product includes the amount of each component in mg/mL, and the amount of each component per bottle to include the overfill. *[Pre-NDA agreement; not a critical issue.]*
10. A justification is provided for the target amount of 12 g as the overfill of formulation per bottle. *[Pre-NDA agreement; not a critical issue.]*

11. Data from the "Simulated Patient Use Study" as proposed:

The simulated patient use study listed in the pre-NDA package (Section 7.0, Attachment 2, under Pharmaceutical Development (3.2.P.2)) has been designed to determine the spray characteristics of the product under uncontrolled conditions representative of the normal dosing regimen (i.e. drug product units are provided to analysts who maintain the units in their possession for thirty (30) days, bringing the units home, to and from work, leaving them in their car, etc., with one dose (two sprays) discharged each day, and testing for key attributes at various intervals with temperature/relative humidity monitoring throughout the study). The purpose of this study is to assess product performance under conditions within the range of label instructions that can be reasonably expected once the product is dispensed to the patient.

PAL's comment: The primary reviewer will evaluate the adequacy of these results in support of the proposed in-use shelf life of 30 days.

- **Critical issue not available at the pre-NDA stage:**

Comparability protocol for changing the drug product pump after NDA approval via a Prior-Approval supplement.

PAL's comment: The primary reviewer will evaluate the adequacy of this proposal.

APPEARS THIS WAY ON ORIGINAL

# Initial Quality Assessment

**Supporting NDA or IND:**  
IND 58346

**Supporting DMF:**

| DMF        | TYPE | HOLDER     | ITEM REFERENCED    | COMMENTS   |
|------------|------|------------|--------------------|--|
| [REDACTED] | II   | [REDACTED] | Cyanocobalamin USP | LOA is provided.<br><br><u>Review is needed.</u><br>The most recent update of the DMF was the 3-MAR-2005 submission which has not been reviewed. The most recent review dated 5-MAR-2004 found the DMF adequate. |
|            | III  |            | [REDACTED]         | LOA is provided.<br><br><u>Review may be needed.</u><br>No review is found for this DMF.   |
|            | III  |            | [REDACTED]         | LOA is provided.<br><br><u>Review is needed.</u><br>The most recent update of the DMF was the 25-AUG-2006 submission, specifically for this combination of spray pump and actuator, which has not been reviewed. |
|            | III  |            | [REDACTED]         | LOA is provided.   |

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## Initial Quality Assessment

| DMF | TYPE | HOLDER | ITEM REFERENCED | COMMENTS   |
|-----|------|--------|-----------------|--|
| 1   | III  | /      | /               | LOA is provided.<br><br><u>Review is not needed.</u><br>Extractables testing being performed on the molded packaging components, not on the _____ Therefore, a safety review of this DMF for the _____ is not necessary. |
|     | III  | /      | /               | LOA is provided.<br><br><u>Review is not needed.</u><br>Extractables testing being performed on the molded packaging components, not on the _____ Therefore, a safety review of this DMF for the _____ is not necessary. |

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**Manufacturers:**

| Responsibility   | Manufacturer Name and Address   |
|--|---|
| Drug Substance<br>Manufacturing, Packaging,<br>Release and Stability Testing,<br>and Release | /   |
| Drug Product Manufacturing,<br>Packaging, Labeling, Release<br>and Stability Testing         | Fleming & Company, Pharmaceuticals<br>1733 Gilsinn Lane<br>Fenton, MO 63026 |
| Contract Laboratory<br>Testing for Particulate Matter  | /   |

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# Initial Quality Assessment

## CHEMISTRY NDA FILEABILITY CHECKLIST

### IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

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

|    | Parameter   | Yes | No | Comment   |
|----|---|-----|----|---|
| 1  | On its face, is the section organized adequately?   | X   |    |   |
| 2  | Is the section indexed and paginated adequately?  | X   |    |   |
| 3  | On its face, is the section legible?  | X   |    |   |
| 4  | Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs? | X   |    |   |
| 5  | Is a statement provided that all facilities are ready for GMP inspection?   | X   |    |   |
| 6  | Has an environmental assessment report or categorical exclusion been provided?  | X   |    |   |
| 7  | Does the section contain controls for the drug substance?   | X   |    | Reference is made to DMF                        |
| 8  | Does the section contain controls for the drug product?   | X   |    |   |
| 9  | Have stability data and analysis been provided to support the requested expiration date?  | X   |    |   |
| 10 | Has all information requested during the IND phase, and at the pre-NDA meetings been included?                                  | X   |    |   |
| 11 | Have draft container labels been provided?  | X   |    |   |
| 12 | Has the draft package insert been provided?   | X   |    |   |
| 13 | Has an investigational formulations section been provided?  | X   |    |   |
| 14 | Is there a Methods Validation package?  | X   |    |   |
| 15 | Is a separate microbiological section included?   | X   |    | Preservative effectiveness testing and results. |

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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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Suong Tran  
11/14/2006 01:57:12 PM  
CHEMIST

as we discussed

Blair Fraser  
11/14/2006 03:06:56 PM  
CHEMIST



ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO DO 19-OCT-2006 10D FERGUSONS  
 DO RECOMMENDATION 20-OCT-2006 ACCEPTABLE SBERRYMA  
 BASED ON FILE REVIEW

PREVIOUS EI OF 7/26-8/3/05 WAS NAI. LIQ PROFILE WAS COVERED AND FOUND ACCEPTABLE. BASED ON FILE REVIEW, KAN-DO RECOMMENDS APPROVABLE.

OC RECOMMENDATION 20-OCT-2006 ACCEPTABLE FERGUSONS  
 DISTRICT RECOMMENDATION

Establishment: CFN FEI

b(4)

DMF No: AADA:

b(4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

| EMilestone Name       | Date        | Type | Insp. Date  | Decision & Reason | Creator     |
|-----------------------|-------------|------|-------------|-------------------|-------------|
| SUBMITTED TO OC       | 19-OCT-2006 |      |             |                   | TRANS       |
| SUBMITTED TO DO       | 19-OCT-2006 | GMP  |             |                   | ADAMSS      |
| ASSIGNED INSPECTION T | 02-NOV-2006 | GMP  |             |                   | ADAMSS      |
| PECTION SCHEDULED     | 29-JAN-2007 |      | 07-FEB-2007 |                   | IRIVERA     |
| INSPECTION PERFORMED  | 07-FEB-2007 |      | 07-FEB-2007 |                   | ERNEST.BIZJ |

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

DO RECOMMENDATION

29-MAR-2007

ACCEPTABLE

ADAMSS

INSPECTION

OC RECOMMENDATION

29-MAR-2007

ACCEPTABLE

ADAMSS

DISTRICT RECOMMENDATION

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APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL