

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203340Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	NYMALIZE (nimodipine) oral solution
Applicant	Arbor Pharmaceuticals, Inc.
Application/Supplement Number	203340
Type of Application	Original
Indication(s)	Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition
Established Pharmacologic Class ¹	dihydropyridine calcium channel blocker
Office/Division	ODE I/DNP
Division Project Manager	Vandna Kishore
Date FDA Received Application	November 20, 2012
Goal Date	May 17, 2013
Date PI Received by SEALD	May 6, 2013
SEALD Review Date	May 7, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Some headings are not centered: Contraindications, W&P, Use in Specific Populations. Also, the horizontal lines should extend across the full width of the column; currently only D&A, DFS and Use in Specific Populations have lines with the correct width.*

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *There should be a "(4)" following the word "None" under Contraindications.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: *There is a typo; this statement currently states: "... safety and effectively" and it must state: "...safely..".*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: The website address is currently in upper case and it should be in lower case.

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: There should not be a period following the heading numbers in TOC. The subheadings for 5.2, 5.3, 5.4 in TOC do not match those in the FPI.

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Selected Requirements of Prescribing Information

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

NO 33. All subsection headings must be indented, not bolded, and in title case.

Comment: Subsection headings are currently bolded and must not be bolded.

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE

Selected Requirements of Prescribing Information

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: The subheading "Carcinogenesis, Mutagenesis, Impairment of Fertility" must have a subsection number: "13.1". This will also affect TOC.

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: The cross references currently do not have the outer brackets italicized; the entire cross-reference should be in italics.

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

ELIZABETH A DONOHOE
05/07/2013

LAURIE B BURKE
05/07/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 203340	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Nymalize Established/Proper Name: nimodipine Dosage Form: Oral Solution Strengths: 60 mg/20mL		
Applicant: Arbor Pharmaceuticals, Inc.		
Date of Receipt: November 20, 2012		
PDUFA Goal Date: May 19, 2013		Action Goal Date (if different): May 17, 2013
Proposed Indication(s): Nymalize is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological conditions (i.e., Hunt and Hess Grades I-IV0).		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO X

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Approved Labeling NDA 18-869 Nimotop Capsule labeling ver 2005.	PLR sections: 1. Indications 2. Dosage and Administration 5. Warnings and Precautions 6. Adverse Reactions 7. Drug Interactions 8. Use in Specific Populations 10. Overdosage 12. Clinical Pharmacology 13. Nonclinical Pharmacology 14. Clinical Studies

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor has requested a waiver of evidence of In Vivo Bioavailability or Bioequivalence under 21 CFR 320.22 (b)(3). The sponsor notes that the currently approved labeling for Nimotop (NDA 18-869) states that studies evaluating the pharmacokinetics of Nimodipine after oral administration have been conducted in patients receiving the drug as capsules, tablets, or an oral solution.

NOTE: The waiver request was discussed with and agreed to by the Agency.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Nimotop (nimodipine) liquid gelatin capsules	NDA 18-869	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

NDA 18-869 Nimotop (nimodipine) Capsules

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support 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 capsule to solution").

This application provides for a change in dosage form, from capsule to solution.

It is important to note that this NDA has been submitted in response to medication errors that have occurred when healthcare professionals have withdrawn the liquid from the approved soft-gel capsule products using a syringe with the intent of administering the medication via a nasogastric tube. However, the contents of the syringe have been inappropriately administered intravenously and multiple deaths have occurred. (See FDA Safety announcements dated August 2 & 19, 2010 for details) The development and marketing of a commercially prepared oral solution has been encouraged by the FDA.

The purpose of the following two questions 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.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(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)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(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 listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(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.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(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) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Nimodipine capsules listed in the Orange book.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) 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.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

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

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

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):

Expiry date(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). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 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):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

VANDNA N KISHORE
04/26/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 3, 2013

To: Vandna Kishore, Regulatory Project Manager
Division of Neurology Products (DNP)

From: Gina McKnight-Smith, Regulatory Review Officer, Team 1
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Team Leader, Team 1
OPDP

Subject: **Comments on draft labeling (PI) for NYMALIZE™ (nimodipine) oral solution, 60mg/20mL NDA #203340**

In response to your consult request dated April 3, 2013, OPDP has reviewed the proposed product labeling (PI) for NYMALIZE™ (nimodipine) oral solution, 60mg/20mL, submitted via email by Vandna Kishore on March 20, 2013. OPDP has taken into consideration the current approved PI for the Reference Listed Drug (RLD) for NIMOTOP® (nimodipine) capsules.

Thank you for the opportunity to review this proposed product labeling. If you have any questions, please contact Gina McKnight-Smith at 301-796-2841.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

GINA P MCKNIGHT-SMITH
04/05/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Review

Date: March 15, 2013

Reviewer: Sue (Liu) Liu, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Nymalize (Nimodipine) Oral Solution
60 mg/ 20 mL

Application Type/Number: NDA 203340

Applicant/sponsor: Arbor Pharmaceuticals

OSE RCM #: 2012-2804

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL (NDA 203340) received on February 11, 2013 (Appendices A through D). The Division of Medication Error Prevention and Analysis (DMEPA) reviewed previous versions of the container labels and carton labeling under OSE Review # 2011-4341 dated March 1, 2012, OSE Review # 2011-4341-1, dated May 16, 2012, OSE Review # 2011-4341-2, dated June 15, 2012, and OSE Review # 2012-2804, dated January 10, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the container labels and carton labeling received on February 11, 2013. We compared the revised labels and labeling against the recommendations contained in our previous labeling reviews for this application.

3 RESULTS

Our review of the revised container labels and carton labeling determined that the Applicant implemented the majority of DMEPA's previous recommendations. However, the following two recommendations were not implemented:

1. [REDACTED] (b) (4) oral syringe
2. [REDACTED] (b) (4) to further reduce clutter

The Applicant requested to implement recommendation 1 at their next printing, rather than upon approval of the application, and submit in the Annual Report since the syringes have been ordered. With regards to recommendation 2, the Applicant will need this information in order to clear customs.

We note that the NDC identification code on the carton labeling and unit-dose cup labels are identical. This is inappropriate since 12 unit-dose cups are packaged in each carton. Therefore, the carton should have a different NDC identification code. We also note that the lot number and expiration date, which were previously on the 16 ounce bottle container label, were inadvertently removed.

4 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container labels and carton labeling determined that the Applicant implemented the majority of DMEPA's previous recommendations. For the recommendations not implemented, we find the Applicant's rationale and proposal acceptable. We identified an additional area of vulnerability with regards to the NDC identification code. Additionally, the Applicant will need to ensure that a lot number and expiration date is included on all labels and labeling. We provide recommendations below, and we advise the recommendations are implemented prior to approval of the application.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions

or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

4.1 COMMENTS TO THE APPLICANT

A. (b) (4) Oral Syringe

1. We have reviewed your request to implement our recommendation to (b) (4) oral syringe at the next printing and submit in the Annual Report since the syringes have been ordered. The recommendation should be implemented within 6 months of approval or at the time of next printing, whichever is sooner.
2. The statement (b) (4) can be retained on the oral syringe.

B. NDC identification code

1. We note the NDC identification codes on the carton labeling and unit-dose cup labels are identical. This is inappropriate since 12 unit-dose cups are packaged in each carton. Therefore, revise the NDC identification code for the carton labeling, and update the "How Supplied" section in the Insert labeling accordingly.

C. 16 Ounce Bottle Container Label

1. We note the lot number and expiration date was on the previously submitted label, but is (b) (4). Ensure the lot number and expiration date are included on the final label for the 16 ounce bottle container.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LIU LIU
03/15/2013

IRENE Z CHAN
03/15/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: January 10, 2013

Reviewer: Liu (Sue) Liu, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Nymalize (Nimodipine) Oral Solution
60 mg/ 20 mL

Application Type/Number: NDA 203340

Applicant/sponsor: Arbor Pharmaceuticals

OSE RCM #: 2012-2804

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Nymalize (Nimodipine) Oral Solution received on June 29, 2012 (see Appendices A through D) and the pre-printed oral syringe received on July 16, 2012 (see Appendix E). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2011-4341 dated March 1, 2012, OSE Review # 2011-4341-1, dated May 16, 2012 and OSE Review # 2011-4341-2, dated June 15, 2012.

2 MATERIAL REVIEWED

DMEPA reviewed the container labels and carton labeling received on June 29, 2012 and the (b) (4) oral syringe received on July 16, 2012. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2011-4341 dated March 1, 2012, OSE Review # 2011-4341-1, dated May 16, 2012 and OSE Review # 2011-4341-2, dated June 15, 2012.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container labels and carton labeling determined that not all of our previous recommendations were implemented by the Applicant. The Applicant (b) (4) on the 16 Ounce Bottle Container Label and Unit-Dose Carton Labeling; (b) (4)

We also identified additional changes that should be made to the container labels and carton labeling to clarify information and improve readability. DMEPA advises the following recommendations be implemented prior to approval of this application:

A. Unit-Dose Carton Labeling

1. (b) (4)
2. The white font of the statement of strength, 60 mg/20 mL, (b) (4)
3. Relocate the statement (b) (4) of strength for increased prominence.
4. The temperature ranges (b) (4) “20°C to 25°C (68°F to 77°F).”

B. Unit-Dose Cup Container Label

Add the statement “For Oral Use Only” under the statement of strength.

C. 16 Ounce Bottle Container Label
See recommendations A.1, A.2 and A.4 above.

D. (b) (4)
See recommendation A.4 above.

E. (b) (4) Oral Syringe

1. (b) (4)

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley at 301-796-5068.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LIU LIU
01/10/2013

IRENE Z CHAN
01/10/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 203340	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Nymalize Established/Proper Name: nimodipine Dosage Form: Oral Solution Strengths: 60 mg/20mL		
Applicant: Arbor Pharmaceuticals, Inc.		
Date of Receipt: November 18, 2011		
PDUFA Goal Date: August 18, 2012		Action Goal Date (if different):
Proposed Indication(s): Nymalize is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological conditions (i.e., Hunt and Hess Grades I-IV0).		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO X

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Approved Labeling NDA 18-869 Nimotop Capsule labeling ver 2005.	PLR sections: 1. Indications 2. Dosage and Administration 5. Warnings and Precautions 6. Adverse Reactions 7. Drug Interactions 8. Use in Specific Populations 10. Overdosage 12. Clinical Pharmacology 13. Nonclinical Pharmacology 14. Clinical Studies

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor has requested a waiver of evidence of In Vivo Bioavailability or Bioequivalence under 21 CFR 320.22 (b)(3). The sponsor notes that the currently approved labeling for Nimotop (NDA 18-869) states that studies evaluating the pharmacokinetics of Nimodipine after oral administration have been conducted in patients receiving the drug as capsules, tablets, or an oral solution. (Waiver request attached)

NOTE: The waiver request was discussed with and agreed to by the Agency at the pre-NDA meeting. (Preliminary minutes attached)

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Nimotop (nimodipine) liquid gelatin capsules	NDA 18-869	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

NDA 18-869 Nimotop (nimodipine) Capsules

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support 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 capsule to solution").

This application provides for a change in dosage form, from capsule to solution.

It is important to note that this NDA has been submitted in response to medication errors that have occurred when healthcare professionals have withdrawn the liquid from the approved soft-gel capsule products using a syringe with the intent of administering the medication via a nasogastric tube. However, the contents of the syringe have been inappropriately administered intravenously and multiple deaths have occurred. (See FDA Safety announcements dated August 2 & 19, 2010 for details) The development and marketing of a commercially prepared oral solution has been encouraged by the FDA.

The purpose of the following two questions 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.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(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)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(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 listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(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.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(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) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Nimodipine capsules listed in the Orange book.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) 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.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

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

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

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):

Expiry date(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). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 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):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

VANDNA N KISHORE
08/02/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Review

Date: June 15, 2012

Reviewer: Jung Lee, RPh
Division of Medication Error Prevention and Analysis

Acting Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL

Application Type/Number: NDA 203340

Applicant: Arbor Pharmaceuticals, Inc

OSE RCM #: 2011-4341-2

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label, carton labeling, amber overwrap labeling, and amber oral syringe for Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL, for revisions resulting from our previous comments to the Applicant in OSE Review #2011-4341-1, dated May 16, 2012, in response to a request from the Division of Neurology Products (DNP).

2 MATERIALS REVIEWED

The revised container labels, carton labeling, (b) (4), and amber oral syringe submitted on May 25, 2012 (See Appendix A to E) as well as OSE Review #2011-4341-1 were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS

Our evaluation of the proposed container labels, carton labeling, and (b) (4) (b) (4) noted continuing needed areas of improvement to clarify correct use of the product. We recommend the following be implemented prior to approval:

3.1 COMMENTS TO THE APPLICANT

A. 16 Ounce Bottle Container Label, 20 mL Unit-Dose Cup Carton Labeling, 20 mL Unit-Dose Cup Label, and (b) (4) the Unit-Dose Cup

1. The proposed product is a solution. The Applicant states that it will not be necessary to (b) (4)

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

REFERENCES

1. OSE Review #2011-4341-1, Final Label and Labeling Review for Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL, May 16, 2012, Lee, J.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JUNG E LEE
06/15/2012

JAMIE C WILKINS PARKER
06/20/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Review

Date: May 16, 2012

Reviewer: Jung Lee, RPh
Division of Medication Error Prevention and Analysis

Acting Team Leader: Chi-Ming (Alice) Tu, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL

Application Type/Number: NDA 203340

Applicant: Arbor Pharmaceuticals, Inc

OSE RCM #: 2011-4341-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label, carton labeling, overwrap labeling and insert labeling for Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL, for revisions to our previous comments to the Applicant in OSE Review #2011-4341, dated March 1, 2012, in response to a request from the Division of Neurology Products (DNP).

2 MATERIALS REVIEWED

The revised container label, carton labeling and insert labeling submitted on March 27, 2012 (See Appendix A to C) and OSE Review #2011-4341 were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective. In addition, on April 19, 2012, an (b)(4) was added to the packaging of the proposed drug product and submitted for review (See Appendix D).

3 DISCUSSION

On March 22, 2012, the Applicant provided samples of the proposed packaging of the unit-dose cups and the enteral feeding syringe (oral syringe) in an (b)(4) packaging. The Applicant stated that each unit-dose cup will be packaged together in an (b)(4) syringe and a package insert. Each carton will contain twelve of these individual (b)(4) packages. An Information Request was sent to the Applicant, dated April 12, 2012, to clarify the statement “(b)(4)” that is printed on the sample syringe. The Applicant responded to the Information Request on April 19, 2012, and stated that because the syringes are being sourced through the company (b)(4) with the statement (b)(4) the syringes intended for (b)(4).

4 CONCLUSIONS

Our evaluation of the proposed Nymalize container label, carton labeling and insert labeling noted areas where information can be improved to minimize the potential for medication errors. We advise the following recommendation be implemented prior to approval:

4.1 COMMENTS TO THE DIVISION

A. INSERT LABELING

1. The Applicant indicated in an email dated March 15, 2012, that an oral syringe will be included with each unit dose cup; therefore, in Section 16, How Supplied/Storage and Handling, we recommend including the statement “Carton of 12 individually wrapped packages containing One 20 mL Unit-Dose Cup and (b)(4).”

B. 16 OUNCE BOTTLE CONTAINER LABELS

1. Currently, the statement (b)(4) is located on the side panel. If the Applicant or Review Division finds the stability or potency of Nymalize will be compromised due to (b)(4), then we recommend relocating (b)(4).

4.2 COMMENTS TO THE APPLICANT

A. GENERAL COMMENTS

1. We suggest labeling the proposed (b) (4), if possible to ensure that (b) (4) is utilized with the proposed Nymalize oral solution.

B. 16 OUNCE BOTTLE CONTAINER LABEL

1. The dosage form, “ORAL SOLUTION,” is in all upper case letters. Revise the presentation of the dosage form to be in title case to improve readability.
2. Revise the statement (b) (4) to “Store at room temperature”.

C. 20 mL UNIT-DOSE CARTON LABELING

1. Revise the net quantity statement on the carton to indicate the unit-dose cups and the (b) (4) syringes are included in the box. For example, “Contains 12 Unit-Dose Cups and (b) (4) Syringes.”
2. Revise the statement (b) (4) to “Store at room temperature”.

D. (b) (4) LABELING

1. Increase the prominence of the proprietary name, established name and statement of strength. Ensure the established name is at least half the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
2. Use consistent wording to describe the accompanying syringe. As currently presented, the container label and carton labeling describe it as “oral syringe” whereas the (b) (4)
3. Revise the statement (b) (4) “Store at room temperature” because post-marketing medication error reports have shown that negative statements such a (b) (4)
4. As currently presented, the text on the labeling appears crowded but there is plenty of space available on the labeling. In order to improve the readability of the (b) (4) labeling, separate the statements on the labeling with a line space such as the example below:



If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

REFERENCES

1. OSE Review #2011-4341, Label and Labeling Review for Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL, March 1, 2012, Lee, J.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JUNG E LEE
05/16/2012

CHI-MING TU
05/16/2012

CAROL A HOLQUIST
05/16/2012

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

/s/

QUYNH-VAN TRAN
05/11/2012

19 Pages of Draft Labeling have been Withheld in Full as b4
(CCI/TS) immediately following this page

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Review

Date: April 23, 2013

Reviewer: Sue (Liu) Liu, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Nymalize (Nimodipine) Oral Solution
60 mg/ 20 mL

Application Type/Number: NDA 203340

Applicant/sponsor: Arbor Pharmaceuticals

OSE RCM #: 2012-2804

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL (NDA 203340) received on April 4, 2013 (Appendices A and B). The Division of Medication Error Prevention and Analysis (DMEPA) reviewed previous versions of the container label and carton labeling under OSE Review # 2011-4341 dated March 1, 2012, OSE Review # 2011-4341-1, dated May 16, 2012, OSE Review # 2011-4341-2, dated June 15, 2012, OSE Review # 2012-2804, dated January 10, 2013, and OSE Review # 2012-2804, dated March 15, 2013

2 MATERIAL REVIEWED

DMEPA reviewed the container label and carton labeling received on April 4, 2013. We compared the revised label and labeling against the recommendations contained in our previous labeling reviews for this application.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container label and carton labeling determined that the Applicant implemented all of DMEPA's previous recommendations. We have no additional recommendations for the container label and carton labeling at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LIU LIU
04/23/2013

IRENE Z CHAN
04/25/2013

REQUEST FOR CONSULTATION

TO (Office/Division): Vera Viehmann, OPS/ New Drug Microbiology

FROM (Name, Office/Division, and Phone Number of Requestor): Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE
March 8, 2012

IND NO.

NDA NO.
203340

TYPE OF DOCUMENT

DATE OF DOCUMENT
November 18, 2011

NAME OF DRUG
Nimodipine Oral Solution

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
asap

NAME OF FIRM: Arbor 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 checked="" type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input 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: NDA 203-340, Nymalize (Nimodipine Oral Solution, 60 mg/20 mL), is a priority NDA (submitted on Nov. 18, 2011). Due to the lack of CMC and Pharm/Tox information, it was decided to be fileable about one and half months ago. During the filing process, we asked the sponsor to provide data to support the proposed target level of methylparaben ((b)(4)). Some of the information in stability studies just came in on Tuesday. With that information plus the previous submitted information, a micro consult is sought.

EDR Location: \\CDSESUB1\EVSPROD\NDA203340\

SIGNATURE OF REQUESTOR
Teshara G. Bouie

METHOD OF DELIVERY (Check one)
 DARRTS EMAIL MAIL HAND

PRINTED 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.

/s/

TESHARA G BOUIE
03/08/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: March 1, 2012
Reviewer: Jung Lee, RPh
Division of Medication Error Prevention and Analysis
Team Leader Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis
Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis
Drug Name and Strength: Nymalize (Nimodipine) Oral Solution, 60 mg/ 20 mL
Application Type/Number: NDA 203340
Applicant/Sponsor: Arbor Pharmaceuticals, Inc
OSE RCM #: 2011-4341

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, carton, and insert labeling for Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL (NDA 203340) for areas of vulnerability that can lead to medication errors in response to a request from the Division of Neurology Products (DNP).

1.1 BACKGROUND

Nimodipine was first approved for US marketing on December 28, 1988 (Nimotop by Bayer Pharmaceuticals, NDA 018869). Generic nimodipine capsules were first approved by FDA on May 2, 2007. On July 8, 2011, Nimotop brand capsules were voluntarily withdrawn from the market by Bayer. Barr Pharmaceuticals' oral nimodipine liquid-filled gelatin capsule is now listed as the Reference Listed Drug (RLD) for nimodipine capsules.

On March 9, 2011 the active moiety of the drug, and not the formulation of the drug, was given orphan-drug designation for the treatment of "subarachnoid hemorrhage from ruptured intracranial berry aneurysms."

In a postmarketing medication error review dated April 8, 2011 (OSE RCM # 2010-1047), DMEPA summarized 31 medication errors associated with nimodipine oral capsules. Postmarketing safety reports on oral nimodipine identified medication errors associated with the use of nimodipine capsules for nasogastric tube administration. In the professional insert labeling, dosing instructions are provided for situations where patients are unable to swallow. The instructions require that the liquid contents of the capsule be extracted into a syringe using a needle. As a result, patients were inadvertently given nimodipine intravenously instead of by mouth or through a nasogastric tube. The use of a needle-fitted syringe containing nimodipine in a health care setting is associated with a significant safety risk of erroneous intravenous administration.

In the postmarketing medication error review, DMEPA made the recommendation to Barr Pharmaceuticals, the manufacturer of the RLD for nimodipine capsules, to "create an oral solution or suspension with an oral dispensing device so that the capsules can be removed from the market."

On November 18, 2011, a different Applicant, Arbor Pharmaceuticals submitted this NDA (203340) for Nymalize (Nimodipine) Oral Solution to address the safety risk with nimodipine capsules. Nymalize is a 505(b)(2) application. The FDA granted Arbor Pharmaceuticals a designation of Fast Track for NDA 203340 on July 20, 2011.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 18, 2011 labeling submission.

- Active Ingredient: Nimodipine
- Indication of Use: A calcium channel blocker indicated in adults for subarachnoid hemorrhage
- Route of Administration: Oral

- Dosage Form: Oral Solution
- Strength: 60 mg/20 mL
- Dose and Frequency of Administration: 20 mL (60 mg) every 4 hours for 21 consecutive days
- How Supplied: 16 oz bottle and 20 mL unit-dose cup, (b) (4)
- Storage: 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)
- Container and Closure Systems:
 - 16 oz Bottle---round, brown, HDPE bottles with white (b) (4) (b) (4) t caps with (b) (4) induction seal foil liners
 - 20 mL Unit-Dose Cup---(b) (4) mL HDPE unit-dose cups (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted November 18, 2011
- Carton Labeling submitted November 18, 2011
- Insert Labeling submitted November 18, 2011

Additionally, since Nimotop is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Nimotop. The AERS search conducted on February 29, 2012 used the following search terms: active ingredient “Nimodipine”, trade name “Nimotop”, and verbatim terms “Nimo%”. The reaction terms used include MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. The time frame of the search was limited to January 1, 2010 to February 29, 2012. January 1, 2010 was used to begin this search because the Postmarketing Medication Error Review for Nimodipine (OSE # 2010-1047) evaluated all Nimodipine medication errors submitted to AERS up until that date.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. In addition, medication errors have been associated with the wrong route of administration of nimodipine capsules. Cases related to the wrong route of administration (IV vs. oral) of nimodipine capsules are considered relevant to our review due to the postmarketing history of this product.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

The AERS search identified two cases which were excluded for the following reasons. One case was previously evaluated in OSE review # 2010-1047. The second case was an inquiry, not a medication error, and it did not involve an actual patient. In this case, the reporter asked why an oral liquid form of Nimodipine has not been developed yet. Following these exclusions we evaluated a total of zero new cases relevant to this review.

3 RESULTS AND DISCUSSION

The following section describes the deficiencies identified in our assessment of the packaging, labels, and labeling.

3.1 DRUG ADMINISTRATION CONCERN

The approval of a nimodipine oral solution will help minimize the risk of intravenous administration of the oral product; however, in patients who require administration through an NG tube, nurses will still be required to draw up the oral solution with a syringe. If an intravenous syringe, and not an oral syringe, is used to draw up the nimodipine oral solution, then the risk for intravenous administration will still exist since a needle can be attached to an intravenous syringe. Therefore, DMEPA recommends that the Applicant provide an oral syringe for drug administration to further minimize the risk of erroneous intravenous administration of oral nimodipine.

3.2 16 OUNCE BOTTLE CONTAINER LABEL

- a) The graphic to the left of the proprietary name is overly prominent and distracts from more important information on the label.
- b) The active ingredient and dosage form comprise the established name but are presented in different fonts.
- c) The strength statement lacks prominence.
- d) The distributor's logo and name as presently stated are overly prominent.
- e) The lot number and expiration date are missing.
- f) The inactive ingredient statement is missing.
- g) Instruction to [REDACTED] ^{(b) (4)} is missing.
- h) Given the history of erroneous intravenous administration with oral nimodipine, the route of administration statement should be made more prominent.
- i) The "Rx Only" statement is overly prominent.

3.3 20 mL UNIT-DOSE CUP CONTAINER LABEL

- a) The label appears cluttered, therefore removal of the "Rx Only", "Protect From Light", and "Package Not Child Resistant" statements will allow for improved readability of more important information.
- b) Instruction to [REDACTED] ^{(b) (4)} is missing.

- c) The net quantity statement is too close to the statement of strength and is redundant information, given the current statement of strength, which may cause confusion.
- d) The proprietary name is in all upper case letters and makes the label difficult to read.

3.4 20 mL UNIT-DOSE CARTON LABELING

- a) See comments 3.2.a) to 3.2.g) above.
- b) The statement “Package Not Child Resistant” is missing.

3.5 INSERT LABELING

- a) Trailing zeros appear throughout the insert labeling.
- b) Units of measure are missing after numbers throughout the insert labeling.
- c) Numbers next to units or symbols are not presented on the same line of text.
- d) Under Section 2.1 (Dosage and Administration), the statement (b) (4) lacks clarity.
- e) Under Section 3 (Dosage Forms and Strengths), it appears the information relating to how Nymalize is supplied is included.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling are unacceptable and introduce vulnerability that can lead to medication errors. We recommend the following recommendations be implemented prior to approval:

A. 16 OUNCE BOTTLE CONTAINER LABEL

1. The graphic to the left of the proprietary name is overly prominent and distracts from more important information on the label. We recommend removing the graphic, or minimizing and moving the graphic away from the proprietary name so that it does not compete in prominence with the proprietary name, established name, and product strength.
2. The active ingredient and dosage form comprise the established name but are presented in different fonts. Ensure the active ingredient and the dosage form are displayed in the same font as the proprietary name.
3. The statement of strength lacks prominence. In order to increase the prominence of the statement of strength, increase the font size.
4. The distributor’s logo and name as presently stated are overly prominent. Decrease the prominence of the distributor’s logo and name on the principal display panel.
5. Ensure the lot number and expiration date are printed on the label.
6. Include the inactive ingredients on the side panel as required under 21 CFR 201.10(a).

7. Instructions to (b) (4) are contained in the package insert labeling but not on the label. Add the statement (b) (4) the principle display panel.
8. Given the history of erroneous intravenous administration with oral nimodipine, the route of administration statement should be made more prominent by increasing the font size.
9. The “Rx Only” statement is overly prominent. Relocate the “Rx Only” statement to a less prominent location and debold.

B. 20 mL UNIT-DOSE CUP CONTAINER LABEL

1. As currently presented, the label appears cluttered. Ensure information required under 21 CFR 201.10(i) is included on the label. To decrease clutter on the label, remove the “Rx Only”, “Package Not Child Resistant”, and “Protect from Light” statements.
2. The net quantity statement is too close to the statement of strength and may cause confusion. Delete the net quantity statement as it is already included with the statement of strength (60 mg/20 mL).
3. The proprietary name is in all upper case letters. Revise the presentation of the proprietary name from all upper case letters (NYMALIZE) to title case (Nymalize) to improve readability. In addition, increase the size of the proprietary name.
4. See comment A.7 above.

C. 20 mL UNIT-DOSE CARTON LABELING

1. See comments A.1 to A.8 above.
2. Include the statement “Package Not Child Resistant.”

D. INSERT LABELING

1. General Comments
 - a. The applicant utilizes trailing zeros within the insert labeling. Trailing zeros can lead to 10-fold errors in dosing. DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes.
 - b. We recommend adding a unit of measure immediately following all numbers, as appropriate. For example under section 14 (Clinical Studies), (b) (4) and (b) (4) mg doses” should be revised to read “30 mg, 60 mg and 90 mg doses.”
 - c. We recommend keeping numbers next to units or symbols within the same line of text. For example under section 8.1 (Pregnancy), 10 mg/kg/day

should all be on one line. Revise the layout so 10 is not at the end of the line of text.

2. Under Section 2.1 (Dosage and Administration), reword the statement ^{(b) (4)} [REDACTED] to read “Refill the syringe with 20 mL of 0.9% saline water solution...” for increased clarity.
3. Under Section 3 (Dosage Forms and Strengths), it appears that information relating to how Nymalize is supplied is included. Consider revising this section so it only includes information pertaining to the dosage form and strength.

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

APPENDICES

Appendix A: AERS Cases Excluded from Further Analysis (n=2)

ISR Numbers	Reason for Exclusion	ISR Numbers	Reason for Exclusion
7638310-7	Wrong Route (IV vs. Oral). Case evaluated in OSE Review # 2010-1047.	6913417-8	Product Label Issue Complaint- The reporter asked the question why an oral liquid form of Nimodipine has not been developed yet after reading an article from Medscape warning against IV administration of Nimodipine. No actual patient was involved.

Appendix C: 16 Ounce Bottle Container Labels



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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

/s/

JUNG E LEE
03/01/2012

IRENE Z CHAN
03/02/2012

CAROL A HOLQUIST
03/02/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203340 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Nymalize Established/Proper Name: nimodipine Dosage Form: oral solution Strengths: 60mg/20ml		
Applicant: Arbor Pharmaceuticals Agent for Applicant (if applicable): n/a		
Date of Application: 11/18/11 Date of Receipt: 11/18/11 Date clock started after UN:		
PDUFA Goal Date: 5/18/11		Action Goal Date (if different): 8/18/12 (with extension)
Filing Date: 1/17/12		Date of Filing Meeting: 12/6/11
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3 (new dosage form)		
Proposed indication(s)/Proposed change(s): SAH, new oral solution of nimodipine		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 110870				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>		x		
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>
--	--

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>
--	---

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
---	-----	----	----	---------

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		x		
--	--	---	--	--

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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		x		
---	--	---	--	--

Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		x		
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>				

Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>			x	
If yes, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
--------------------	-----	----	----	---------

Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/loopd/index.cfm</i>		x		
---	--	---	--	--

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>		x		
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		x		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		x		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>		x		

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) xCTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	x			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	x			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	x			

¹
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	x			N/A as clinical studies were not performed.
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	x			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	x			

<p>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</p> <p><i>Note: Debarment Certification should use wording in FDCA 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...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	x			

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			x	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		x		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			x	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			x	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			x	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		x		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	x			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>			x	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	x			
Is the PI submitted in PLR format? ⁴	x			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	x Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	x			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	x			
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			x	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	x			
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>			x	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		x		

<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/30/12 scheduled but cancelled after preliminary comments sent</p> <p><i>If yes, distribute minutes before filing meeting</i></p>		x		See DARRTS record under IND 110870 for prelim comments.
<p>Any Special Protocol Assessments (SPAs)? Date(s):</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>		x		

ATTACHMENT
(See attached info on filing meeting)
MEMO OF FILING MEETING

DATE: 12/6/11

BLA/NDA/Supp #: 203340

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME:

DOSAGE FORM/STRENGTH:

APPLICANT:

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:		
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:		
	TL:		
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:		
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> ● Abuse Liability/Potential <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> ● 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? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> ● Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CMC Labeling Review	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority:	
21 st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	<ul style="list-style-type: none"> notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

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 OND ADRA or OND IO.

Filing Meeting Description and Agenda Template

12/16/11

NDA 203340 Nimodipine Oral Solution

1. Team Introductions
2. Introduction of application, including important dates

Summary Description of Product:

NDA 203340, Nimodipine oral solution, by Arbor Pharmaceuticals for the indication of Subarachnoid Hemorrhage.

An electronic link to the application: EDR Location:

\\CDSESUB1\EVSPROD\NDA203340\203340.enx

This has a Fast Track and Orphan Drug Designation

PIND #110870

PDUFA goal date is May 18, 2012 (Priority Review timeline possibly-Will determine designation at this meeting)

Stamp Date: 18-Nov-2011

Filing Date: **60-day filing letter due date is January 17, 2012**

Day 74 Letter Date: 74 day letter due date is January 31, 2012

IMPORTANT Goal Dates according to GRMP:

Filing/Planning meeting by Day 30: Dec 18, 2011

Mid-cycle meeting to be scheduled by Month 3: Feb 18, 2012

Reviews complete 3.5 weeks before action date: Apr 24, 2012

Send proposed labeling to applicant 3 weeks prior action: Apr 27, 2012

Wrap up meeting 4 weeks prior action: Apr 20, 2012

Compile/circulate action letter/package to DD: May 4, 2012

ACTION DATE: May 18, 2012

3. Overview of Application/RTF Issues, if any, by Discipline: Studies/info submitted; identification of Info Requests; Day 74 letter items
 - a. CMC-Martha Heimann/Donhau Lu; Biopharmaceutics-Kareen Rivierre
 - b. DSI-Tony El-Hage
 - c. P/T – Richard Siarey
 - d. Clin Pharm/Biopharm – Xinning Yang
 - e. Clinical –John Marler/Billy Dunn
 - f. Stats – Kun Jin?
 - g. OSE-DMEPA- Jung Lee, Irene Chan; DPV-Cindy Kortepeter; OSE-DRISK- None(no REMS)
 - h. DDMAC-Quynh Van Tran; Sharon Watson
 - i. PLT-none(no patient labeling)
 - j. Anyone else?
4. Reach agreement on filing decision

Fileable

Filing Meeting Description and Agenda Template

The NDA/BLA filing meeting has multiple purposes

- Review label to identify significant issues for the Filing Communication (74-day letter)
- Plan the review strategy (e.g., review schedule, team meetings, involvement of consultants, Advisory Committee)
- Plan what will be completed by the mid-cycle meeting (interim deliverables) for presentation/discussion

Meeting Attendees: Attendees include primary reviewers, team leaders, CDTL, RPM, Division Director/Deputy (OND), office director (if the office director is the signatory authority), Division Director/Deputy of discipline offices when determined appropriate. Representatives from DDMAC, DSI, DMPQ, and OSE are also generally invited; however, if they cannot attend they will often provide comments for the meeting discussion. Attendees may also include already identified consultants (e.g., Controlled Substances Staff).

Team members come to the meeting prepared with completed filing review checklists, overviews of application modules, and potential issues. This preparation is critical to a focused discussion on filing, needed information requests, and review issues as well as decisions on review priority, chemical classification, and for planning the review time line. All team members should be encouraged to communicate with other team members, including their project manager and team leader as soon as problems are identified. Team members should be encouraged to ask questions and discuss any concerns throughout the review process so that issues are identified and discussed as soon as possible.

Meeting Agenda: An agenda for the filing/planning meeting should be provided to the team members prior to the meeting. In the event there are new team members, the review team should introduce themselves to each other and briefly discuss how review team meetings will be conducted and how administrative decisions will be made. The CDTL chairs the meeting and the RPM acts as facilitator and is also responsible for meeting minutes.

At the filing meeting, each reviewer makes presentations on the high-level contents and fileability of their review section and presents his/her findings thus far. During the meeting, each reviewer discusses the relevant content of the application covering the following:

- A summary of the application relevant to their discipline
- Any special issues
- A description of any material needed for the review not included in the application
- Any deficiencies that may warrant a refusal to file decision
- Other substantive deficiencies that may have an impact on their ability to complete the review or approve the application (to be transmitted in the Filing Communication)
- Issues that merit advisory committee input
- Confirmation of the standard/priority review decision
- Need for any additional consult reviews

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 203340

Type of Application: Original NDA

Name of Drug: Nimodpine oral solution

Proposed Indication: Treatment of subarachnoid hemorrhage

Applicant: Arbor Pharmaceuticals

Labeling Reviewed

Submission Date: 11/18/11

Receipt Date: 11/18/11

Background and Summary Description

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies within XX weeks. The resubmitted labeling will be used for further labeling discussions. The sponsor should address the following issues in their proposed nimodipine oral solution:

Highlights

1. Consider removing the trademark symbols throughout the label.
2. Bold the entire product title line and use undercase for the dosage form.
3. Include the correct pharmacologic class for nimodipine

4. Do not repeat the (b) (4) under the Dosage and Administration heading.
5. Remove the word (b) (4) Contraindications heading
6. Consider including “edema” and “headaches” in the Adverse Reactions list.
7. Only include clinically significant Drug Interactions.

Table of Contents

8. Remove subsections 1.1, 2.1, and 14.1 because there are no subsections 1.2, 2.2, or 14.2.

Full Prescribing Information

9. Revise the Dosage and Administration subsection to include subsections and avoid bolding and use of uppercase.
10. Use appropriate cross-referencing (see Implementation Guidance at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf>)
11. Make sure that all Warnings and Precautions regarding dihydropyridine calcium channel blockers are included (e.g., edema) in the Warnings and Precautions section.
12. Recommend that verbiage is not capitalized and the use of bold is minimized.
13. The title of Warnings and Precautions should be specific to the adverse reactions; it should not be “General.”
14. Include the following statement in Section 6.1: “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
15. All tables should include a title.
16. Nimotop (nimodipine capsules) have been marketed for over 20 years; spontaneous adverse reactions associated with Nimotop could be included in a Postmarketing Experience subsection.
17. Only clinically significant Drug Interactions should be included.
18. For the Patient Counseling Information section, use command language and include all important information that a prescriber should tell a patient.

Vandna Kishore, R.Ph 1/28/12
Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical format issues during labeling development and review. In this SRPI review, only identified deficiencies are checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and bold type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading - if no contraindications are known, it must state "None")
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) — 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) — removal 2/2010.”

- **Indications and Usage**
 - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
- **Contraindications**
 - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
 - All contraindications listed in the FPI must also be listed in HL.
 - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
 - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.
- **Adverse Reactions**
 - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
 - For drug products other than vaccines, the verbatim bolded statement, “To report **SUSPECTED ADVERSE REACTIONS**, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch” must be present. Only include toll-free numbers.
- **Patient Counseling Information Statement**
 - Must include the verbatim statement: “See 17 for Patient Counseling Information” or if the product has FDA-approved patient labeling: “See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).
- **Revision Date**
 - A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in **UPPER CASE** and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**
 - A horizontal line must separate the TOC and FPI.
 - The heading - **FULL PRESCRIBING INFORMATION** - must appear at the beginning in **UPPER CASE** and **bold** type.
 - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
 - Must have a heading, in **UPPER CASE**, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
 - Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
- **Contraindications**
 - For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”