

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202236Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 202236	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: DYMISTA		
Established/Proper Name: azelastine hydrochloride and fluticasone propionate		
Dosage Form: Nasal Spray		
Strengths: 137 mcg / 50 mcg (0.1%/0.037%)		
Applicant: Meda Pharmaceuticals		
Date of Receipt: April 1, 2011		
PDUFA Goal Date: May 1, 2012		Action Goal Date (if different):
Proposed Indication(s): Seasonal Allergic Rhinitis in patients 12 years of age and older		

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

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)
Flonase NDA 20121	Label Sections: 5.3, 6.2, 7.2, 7.5, 8.1, 8.3, 8.4, 10, 11, 12.1, 12.3, 13.1, 13.2, 17.9

*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 Applicant conducted two pharmacokinetic studies bridging the proposed product to the reference products. Trial X-03065-3282 evaluated the proposed product, the investigational fluticasone propionate monotherapy, and commercially available fluticasone propionate. Trial X-03065-3283 evaluated the proposed product, the investigational azelastine hydrochloride product, and commercially available azelastine hydrochloride.

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)
Flonase	NDA 20121	Y

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:

- 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 new nasal spray combination.

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):

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

Drafted by: Bowen/11-21-11

505b2 Clearance: Bertha/3-30-12
Duvall/3-30-12
Ripper/3-30-12

Finalized: Jackson/5-1-12

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/s/

COLETTE C JACKSON
05/01/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 202-236
Product Name: Dymista (azelastine hydrochloride and fluticasone propionate) Nasal Spray,
137 mcg / 50 mcg

PMR/PMC Description: Long-term safety trial in children 4 to 11 years of age with seasonal allergic rhinitis or perennial allergic rhinitis.

PMR/PMC Schedule Milestones: Final Protocol Submission: 10/2012
Study/Trial Completion: 02/2014
Final Report Submission: 06/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and efficacy in patients 12 years and older have been established.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Evaluate long-term safety in children 4 to 11 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, parallel-group, placebo- or active-controlled, 3-month safety trial evaluating Dymista Nasal Spray in approximately 400 children 4-11 years of age.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Primary safety trial
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
04/30/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 202-236
Product Name: Dymista (azelastine hydrochloride and fluticasone propionate) Nasal Spray,
137 mcg / 50 mcg

PMR/PMC Description: Efficacy and safety trial in children 4 to 11 years of age with seasonal allergic rhinitis.

PMR/PMC Schedule Milestones: Final Protocol Submission: 02/2013
Study/Trial Completion: 12/2013
Final Report Submission: 06/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and efficacy have been established in patients 12 years and older.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Evaluate efficacy and safety in children 4 to 11 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

<p>(b) (4) trial in children 4 to 11 years of age with seasonal allergic rhinitis.</p>
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Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
04/30/2012

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

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

Memorandum

Date: November 25, 2011

To: Philantha Bowen, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matthew Falter, PharmD, Regulatory Review Officer, Division of
Direct-to-Consumer Promotion (DDTCP), Office of Prescription
Drug Promotion (OPDP)
Roberta Szydlo, R.Ph., Regulatory Review Officer, Division of
Professional Promotion (DPP), OPDP

CC: Robyn Tyler, Group Leader, DDTCP
Lisa Hubbard, Group Leader, DPP
Michael Wade, Regulatory Health Project Manager, OPDP
Olga Salis, Regulatory Health Project Manager, OPDP

Subject: NDA # 202236
OPDP labeling comments for DYMISTA (azelastine hydrochloride
and fluticasone propionate) Nasal Spray

OPDP has reviewed the proposed Package Insert (PI), Patient Package Insert (PPI), Patient's Instructions for Use (IFU), and Carton and Container labeling for DYMISTA (azelastine hydrochloride and fluticasone propionate) Nasal Spray submitted for consult on May 2, 2011.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "NDA 202236-DPARPs Draft Label(EDITED 11-14-11).doc", which was sent via email from DPARP to OPDP on November 15, 2011. OPDP's comments on the proposed PI are provided directly in the marked-up document attached (see below).

OPDP's comments on the PPI and IFU are based on the proposed draft marked-up labeling titled "NDA 202236 DMPP PPI-IFU (clean).doc" which was sent via email from the Division of Medical Policy Programs (DMPP) to OPDP on November 22, 2011. OPDP agrees with DMPP's recommendations on the

proposed PPI and IFU and offers the following comments provided in the marked-up document attached (see below).

OPDP's comments on the proposed carton and container labeling are based on the labeling submitted by the sponsor on July 1, 2011, and located in the EDR at:

- [\\cdsesub1\EVSPROD\NDA202236\0003\m1\us\114-label\1141-draft-label\carton-6g-sample-carton.pdf](#)
- [\\cdsesub1\EVSPROD\NDA202236\0003\m1\us\114-label\1141-draft-label\carton-23g-trade-carton.pdf](#)
- [\\cdsesub1\EVSPROD\NDA202236\0003\m1\us\114-label\1141-draft-label\carton-6g-sample-label.pdf](#)
- [\\cdsesub1\EVSPROD\NDA202236\0003\m1\us\114-label\1141-draft-label\carton-23g-trade-label.pdf](#)

We offer the following comments on the proposed carton and container labeling:

Carton

- The Dosing Instructions presented on the side panel of the carton do not contain all of the steps for properly administering Dymista Nasal Spray as presented in the Instructions for Use. We are concerned that this presentation may be misleading if presented in a promotional context. If this information is not considered essential, we recommend that it be removed and replaced with a directive instructing patients to carefully read the enclosed Patient's Instructions for Use.
- We recommend that the established name be presented in manner consistent with 21 CFR 201.10(g)(2) which requires that the established name be at least half the size of the letters comprising the proprietary name and have a prominence consistent with the proprietary name in terms of type, size, color, and font.

Container

- We recommend that the established name be presented in manner consistent with 21 CFR 201.10(g)(2) which requires that the established name be at least half the size of the letters comprising the proprietary name and have a prominence consistent with the proprietary name in terms of type, size, color, and font.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the PI or Carton and Container Labeling, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

If you have any questions regarding the PPI or the IFU, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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

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/s/

ROBERTA T SZYDLO
11/25/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **November 21, 2011**

To: **Badrul Chowdhury, M.D., Ph.D., Director
Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: **LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)**
**Melissa Hulett MSBA, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs**

From: **Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs**

Subject: **DMPP Review of Patient Labeling (Patient Package Insert,
Instructions for Use)**

Drug Name (established name): **Dymista (azelastine hydrochloride 0.1% and fluticasone propionate 0.037%)**

Dosage Form and Route: **Nasal Spray**

Application Type/Number: **NDA 202236**

Applicant: **Meda Pharmaceuticals**

1 INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU), for Dymista (azelastine hydrochloride 0.1% and fluticasone propionate 0.037%) nasal spray. The purpose of the Applicant's submission is to obtain initial approval for azelastine hydrochloride 0.1% and fluticasone propionate 0.037% nasal spray for the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older.

2 MATERIAL REVIEWED

- Draft, Dymista (azelastine hydrochloride 0.1% and fluticasone propionate 0.037%) nasal spray, PPI and IFU received on April 1, 2011 and revised by the Review Division throughout the review cycle and received by DMPP on May 9, 2011.
- Draft, Dymista (azelastine hydrochloride 0.1% and fluticasone propionate 0.037%) nasal spray, Prescribing Information (PI) received April 1, 2011 revised by the Review Division throughout the current review cycle and received by DMPP on May 9, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the prescribing information (PI)
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI and IFU are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

25 Pages 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/

TWANDA D SCALES
11/22/2011

MELISSA I HULETT
11/22/2011

LASHAWN M GRIFFITHS
11/22/2011

**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: October 26, 2011

Reviewer: Yelena Maslov, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, Pharm.D., Team Leader
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Dymista
(Azelastine HCl and Fluticasone Propionate) Nasal Spray,
137 mcg/50 mcg per Spray

Application Type/Number: NDA 202236

Applicant/sponsor: Meda Pharmaceuticals Inc.

OSE RCM #: 2011-1425

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

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis's (DMEPA's) evaluation of the proposed product packaging as well as container label, carton labeling, prescribing information, and instructions for use (IFU) of Dymista Nasal Spray for vulnerabilities to confusion that may lead to medication errors.

1.1 REGULATORY HISTORY

Dymista Nasal Spray (NDA 202236) is a subject of a 505(b)(2) application referencing Astelin (Azelastine Hydrochloride) Nasal Spray and Flonase (Fluticasone Propionate) Nasal Spray. The Application was submitted to the FDA on April 1, 2011. DMEPA found the name Dymista acceptable on July 14, 2011.

1.2 PRODUCT INFORMATION

Dymista (Azelastine Hydrochloride and Fluticasone Propionate) Nasal Spray is indicated for the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. Dymista will be available at the strength of 137 mcg/50 mcg per Spray. Dymista should be administered as one spray per each nostril twice daily. It will be available in nasal spray pump units containing 120 metered sprays (trade size) or 28 metered sprays (sample size).

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, the principles of human factors, and lessons learned from the post-marketing experience, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted on July 1, 2011 (Appendix A)
- Carton Labeling submitted on July 1, 2011 (Appendix B)
- Insert Labeling submitted on July 1, 2011 (no image)

Additionally, since the reference listed drug products, Astelin and Flonase are currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Astelin or Flonase. The July 26, 2011, AERS search used the following search terms: active ingredient "Azelastine", trade names "Astelin" and "Flonase", and verbatim terms "Astel%", "Azelast%", "Flona%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". No time limitations were set.

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.

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

Reports excluded from the case series include those that did not describe a medication error (i.e., adverse event, lack of efficacy, allergic reaction), or reported medication errors not related to the labels and labeling (i.e., accidental eye exposure or overdose due to inadequate relief of symptoms), or reported medication errors involving a concomitant medication or different drug product containing the same active ingredient (e.g., Flovent, Advair, or Optivar).

3 RESULTS

Following exclusions we evaluated a total of three cases (n=3). One case (n=1) involved Flonase Nasal Spray and two cases (n=2) involved Astelin Nasal Spray.

The following section describes the medication errors identified in detail.

3.1 FLONASE MEDICATION ERRORS

DMEPA evaluated one case (n=1) involving wrong route of administration of Flonase Nasal Spray. The case (n=1, ISR #6010204-2) reported administering Flonase into the ear. The case did not provide the contributing factors. Patient developed a rash on his face. This type of error may be indicative of the errors that may occur with Dymista. Thus, it is important to emphasize the correct route of administration on the labels and labeling, which will be discussed in Section 4.

3.2 ASTELIN MEDICATION ERRORS

DMEPA evaluated two cases (n=2) involving wrong administration technique of Astelin Nasal Spray. Both cases (n=2, ISR 2001398 and 5125200-7) reported administration of Astelin with the head tilted back, which resulted in throat burning and irritation. Since Dymista's patient information labeling, instructions for use, and carton labeling clearly state to tilt the head down to keep the medication going to the throat, the cases were not evaluated further.

4 DISCUSSION

Dymista will be supplied in a nasal pump device that will contain a bottle with a nasal applicator. To be activated, the nasal applicator should be pressed. The proposed product design is acceptable for a nasal formulation. It does not represent a source of confusion due to pointed nasal application and similarity to marketed devices for other nasally administered H1-receptor antagonists or corticosteroids.

However, during the meetings held on August 29, 2011 and October 5, 2011, the CMC reviewer and the clinical team noted that the device appears "flimsy" because when the dust cap is removed, the spray pump unit comes off. After the device is re-assembled, the spray pump unit can be potentially depressed. DMEPA cannot specifically comment on the flimsiness of the components and whether they meet the specifications since this is outside of our expertise. Thus, CDRH should be consulted to address this issue. Additionally, if this problem may affect usability of the product, additional instructions for use in the prescribing information as well as IFU labeling should be included, so that patients know what to do in the event of the spray pump unit separates from the bottle.

Additionally, DMEPA identified several deficiencies with the container label, carton labeling, and instructions for use that may be vulnerable to confusion and may lead to medication errors. We discuss these deficiencies in sections below.

4.1 CONTAINER LABELS

The container label can be improved to help minimize the potential for medication errors. DMEPA identified a wrong route medication error involving a similar product, Flonase, being administered in the ear. Thus, it is important to indicate the correct route of administration on the labels and labeling. The principle display panel contains (b) (4)

[REDACTED]

the statement “For intranasal Use Only” should be prominent. (b) (4)

[REDACTED]

Furthermore, the important statement “Shake the bottle gently before each use” is located on the side panel and does not appear prominent. However, the principle display panel contains a statement “US patent pending”. The principle display panel of Dymista should only contain the most important information for correct administration of the product such as proprietary and established names, dosage form, strength, route of administration, and special instructions. Additional information not pertinent to the correct product administration should be relocated to the side panel.

The container label also appears cluttered. As a result, it is important information such as proprietary and established names, dosage form, strength, and route of administration may be overlooked. Thus, the container label should be revised to help emphasize the important information.

4.2 CARTON LABELING

Carton labeling can also be improved to increase the prominence of the correct route of the administration. Currently, the route of administration is located on the bottom of the front panel in small letters immediately [REDACTED] (b) (4)

Additionally, the carton labeling contains incomplete priming instructions, which is misleading and may result in medication errors. Thus, the priming instructions should be revised to provide full details for the correct priming of the device. Additionally, the priming instructions are located on a side panel along with other storage and the general usual dose information and can be easily overlooked. Thus, these instructions should be moved to the side panel that contains specific dosing instructions. Furthermore, the illustrations can be improved by printing them in color to aid consumer readability and comprehension of the dosing instructions.

4.3 INSTRUCTIONS FOR USE (IFU)

Instructions for Use (IFU) contain inconsistent terminology when referring to the parts on the nasal spray device. For example, (b) (4) is also referred to as dust cap and “spray pump unit” is also referred to as (b) (4). This is confusing and may result in misidentification of the parts. Thus, the IFU should be revised to use consistent terminology throughout the entire IFU.

Additionally, the *Clean the Spray Tip* Section does not contain any illustrations to aid consumers’ comprehension of the instructions. Thus, the illustration should be added to provide clarity of the process.

5 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed product design of a nasal spray is appropriate for this drug. However, the container label, carton labeling, prescriber information labeling, and instructions for use introduce vulnerability that can lead to medication errors and thus, should be improved. We provide recommendations below to aim at reducing the risk of medication errors. Section 5.1 *Comments to the Division* contains our recommendation regarding prescriber information labeling and instructions for use (IFU). Section 5.2 *Comments to the Applicant* contains our recommendations regarding container label and carton labeling. We request our comments be communicated to the Applicant prior to approval. If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

5.1 COMMENTS TO THE DIVISION

A. Package Insert Labeling

1. General Comments

- a. Revise the presentation of the proprietary name from all upper case letters (DYMISTA) to title case (Dymista) to improve readability.

- b. (b) (4)
The strength should appear outside of the parentheses that contains the established name after the dosage form. Revise the presentation of the strength, (b) (4) as follows:

*Dymista (Azelastine Hydrochloride and Fluticasone Propionate) Nasal Spray,
137 mcg/50 mcg per spray*

2. Section 2, Dosage and Administration

Revise this Section to relocate the sentence “Administer Dymista Nasal Spray by the intranasal route only” from Section 2.2 to Section 2.1 after the first sentence. We recommend this change because this important administration information should be more prominent by being states next to dosing information.

3. Section 2.2 *Important Administration Instructions* and Section 17, *Patient Counseling Information*

We recommend adding instructions for use regarding what steps should be taken to correctly use and administer the medication in the event of the spray pump unit separates from the bottle. Additionally, we recommend adding the instructions regarding what steps should be taken if the product is accidentally sprayed in the eyes.

B. Instructions for Use (IFU) Labeling

1. General

- a. Revise the presentation of the proprietary name from all upper case letters (DYMISTA) to title case (Dymista) to improve readability.
 - b. Add the instructions for use regarding what steps should be taken to correctly use and administer the medication in the event of the spray pump unit separates from the bottle.
2. As currently presented, IFU uses inconsistent terminology when referring to different parts of the nasal spray pump unit, which is confusing and may lead to misidentification of the unit's parts. Thus, ensure you use consistent terminology when referring to the parts of the device throughout the Instructions for Use (IFU). For example:
- Figure 1 uses the term [REDACTED] (b) (4) but in Step 2 *To Prime* Section, the cap is referred to as “dust cap”. Additionally, the *Clean the Spray Tip* Section reverts to the term [REDACTED] (b) (4)
 - Figure 1 uses the term “spray pump unit”, but in *Clean the Spray Tip* Section, [REDACTED] (b) (4). If these statements refer to different parts on the device, then revise Figure 1 to ensure it contains clear images and labels for both of these parts.
3. The *Dosage and Administration* Section states that Dymista's bottle should be shaken gently before each use. Therefore, we request you revise the statement [REDACTED] (b) (4) in Step 3 of *To Use Dymista Nasal Spray* Section to state “Shake the bottle gently and place the spray tip ¼ to ½ inch into one nostril”.
4. Add illustrations to Section *To Clean the Spray Tip* to aid consumer understanding of the cleaning instructions.
5. Revise the statement [REDACTED] (b) (4) to clarify what part of the device should be pulled upwards. As currently stated, the statement is unclear and confusing because [REDACTED] (b) (4)

5.2 COMMENTS TO THE APPLICANT

A. Carton Labeling (6 g, Sample Size and 23 g, Trade Size)

1. Ensure the size of the established name is at least ½ size of the letters comprising the proprietary name and has prominence consistent with the proprietary name including type, size, color, and font in accordance with 21 CFR 201.10(g)(2).

2. [REDACTED] (b) (4)
- Thus, revise the presentation of the strength, [REDACTED] (b) (4) as follows:

Dymista
(Azelastine Hydrochloride and Fluticasone Propionate) Nasal Spray
137 mcg/50 mcg per Spray

3. Revise the presentation of the proprietary name from all upper case letters (DYMISTA) to title case (Dymista) to improve readability.
4. Ensure the strength of the product (i.e., 137 mcg/50 mcg per spray) is more prominent than the product’s net quantity (i.e., 28 Metered Sprays” or “120 Metered Sprays”) by decreasing the font size of the net quantity [REDACTED] (b) (4)
5. [REDACTED] (b) (4) Additionally, this [REDACTED] (b) (4) distracts from the most important information such as proprietary and established name, dosage form, and strength. Thus, revise the background color to improve contrast and readability of the information.
6. Increase the prominence of the route of administration “FOR INTRANASAL USE ONLY” by relocating it to a more prominent location underneath the dosage form and strength of the product and by increasing the font size. Additionally, place the route of administration on all panels that contain product’s name (i.e., panels with green color).
7. Delete the statement [REDACTED] (b) (4)
8. Add the statement “Shake the bottle gently before each use” to the principle display panel.
9. [REDACTED] (b) (4) We request you delete [REDACTED] (b) (4)
10. Relocate the amount of active ingredient delivered in each spray statement on the side panel to appear above the list of the inactive ingredient. This will make the active ingredient statement more prominent and easier to locate.
11. Revise the statement [REDACTED] (b) (4) to read “Initial priming: 6 sprays or until a fine mist appears”. Additionally, revise the statement [REDACTED] (b) (4) to read “Repriming (only if you have not used Dymista for 14 or more days): 1 spray or until a fine mist appears.” As currently

presented, the instructions are incomplete and misleading. This may be misinterpreted and lead to errors.

12. If space permits, relocate the priming instructions prior to dosing instructions to the back panel. However, if not feasible to relocate, increase the prominence of the priming instructions by increasing the font size and relocating additional information on that panel to the empty panel.
13. Provide illustrations in *Dosing Instructions* in color to help to increase readability and comprehension of instructions.
14. Add an additional step prior to the statement “Spray once per nostril” that reads “Shake the bottle gently”.
15. Delete the statement [REDACTED] (b) (4)
16. Relocate the bar code to the empty panel from the bottom panel of the carton labeling because it can get worn or overlooked at the bottom of the box.

B. Container Label (6 g, Sample Size and 23 g, Trade Size)

1. Ensure the size of the established name is at least ½ size of the letters comprising the proprietary name and has prominence consistent with the proprietary name including type, size, color, and font in accordance with 21 CFR 201.10(g)(2).
2. [REDACTED] (b) (4)
[REDACTED] (b) (4)
Thus, revise the presentation of the strength, [REDACTED] (b) (4)
as follows:

Dymista
(Azelastine Hydrochloride and Fluticasone Propionate) Nasal Spray
137 mcg/50 mcg per Spray
3. Revise the presentation of the proprietary name from all upper case letters (DYMISTA) to title case (Dymista) to improve readability.
4. Revise the net quantity to state “Delivers 28 Metered Sprays” or “Delivers 120 Metered Sprays” to ensure consistency with carton labeling and to increase clarity of the statement.
5. Relocate the net quantity “Delivers 28 Metered Sprays” or “Delivers 120 Metered Sprays” away from the products strength (i.e., 137 mcg/50 mcg per spray) as the net quantity may be misinterpreted as the strength of the product. Additionally, ensure the strength of the product (i.e., 137 mcg/50 mcg per spray) is more prominent than the product’s net quantity (i.e., 28 Metered Sprays” or “120 Metered Sprays”).
6. Delete the statement [REDACTED] (b) (4)

(b) (4)

7. Decrease the prominence of the phrases “6 g” or “23 g” by decreasing font size and relocating to the less prominent location as these statements are as prominent as the strength of the product.
8. Decrease the prominence of the statement “Rx only” by debolding, decreasing the font size, and relocating to less prominent location as this statement is as prominent as the established name of the product.
9. Relocate the statement “Each spray delivers 0.137 mL (137 mcg Azelastine hydrochloride and 50 mcg Fluticasone propionate)” to the side panel as this statement clutters the principle display panel. Only the most important information should appear on the principle display panel.
10. Delete the [REDACTED] (b) (4)
11. Delete or relocate the statement “U.S. Patent Pending” to the side panel. Only the most important information should appear on the principle display panel.
12. Delete the statement [REDACTED] (b) (4)

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

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/s/

YELENA L MASLOV
10/26/2011

ZACHARY A OLESZCZUK
10/27/2011

CAROL A HOLQUIST
10/31/2011

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 # 20236 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: DYMISTA Established/Proper Name: azelastine/fluticasone Dosage Form: Nasal Spray Strengths: azelastine hydrochloride 0.1% and fluticasone propionate 0.037%		
Applicant: Meda Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: April 1, 2011 Date of Receipt: April 1, 2011 Date clock started after UN:		
PDUFA Goal Date: February 1, 2012	Action Goal Date (if different):	
Filing Date: May 31, 2011	Date of Filing Meeting: May 13, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): Seasonal Allergic Rhinitis in patients 12 years of age and older.		
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:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 <i>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 checked="" type="checkbox"/> Standard <input 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 checked="" 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 checked="" 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 type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input 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): 77363				
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>	✓			
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>	✓			
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>	✓			
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>				
<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?	✓			

<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 checked="" type="checkbox"/> Paid <input 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>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>✓</p>																		
<p>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)].</p>		<p>✓</p>																		
<p>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)]?</p> <p><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></p>		<p>✓</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>✓</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>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.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>✓</p>																		

<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>				
<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: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	✓			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		✓		
<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>				

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) <input checked="" type="checkbox"/> CTD <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>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<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>	✓			

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" 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)?	✓			
<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?	✓			
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)?	✓			
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)?	✓			
<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?	✓			
<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?	✓			

<p><i>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].</i></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>			✓	<i>Electronic Submission</i>

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>			✓	

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>	✓			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	✓			

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>	✓			
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>		✓		
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>		✓		
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>	✓			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		✓		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" 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 in 74-day letter.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			

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 PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> 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>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
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>	✓			<i>Micro Consult – CMC RPM conveyed responsibility in completing the request</i>
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): <i>If yes, distribute minutes before filing meeting</i>		✓		<i>No EOP2, however other meeting are noted: Minutes dated 7/10/07 and 10/4/07</i>

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Minutes dated 9/10/10 <i>If yes, distribute minutes before filing meeting</i>	✓			
Any Special Protocol Assessments (SPAs)? Date(s): SPA Denied – Minutes dated 5/19/08 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	✓			

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 13, 2011

NDA: 202236/0

PROPRIETARY NAME: DYMISTA

ESTABLISHED/PROPER NAME: azelastine/fluticasone

DOSAGE FORM/STRENGTH: Nasal Spray

APPLICANT: Meda Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): SAR in adults 12 years of age and older

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Philantha Bowen	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Susan Limb		
Clinical	Reviewer:	Jennifer Pippins	Y
	TL:	Susan Limb	Y
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:	Lokesh Jain	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Feng Zhou	Y
	TL:	Joan Buenconsejo	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcie Wood	Y
	TL:	Timothy Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Eugenia Nashed	Y
	TL:	Prasad Peri	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Yelana Maslov	N
	TL:	Zachary Oleszczuk	N
OSE/DRISK	Reviewer:	Twanda Scales	N
	TL:	Melissa Hulett	N
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	DPV: Dipti Kalar (safety evaluator) Ann Corken MacKay (TL)		N
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <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 checked="" 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 checked="" 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
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" 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: <i>Initial review of the application does not raise any data integrity concerns. It does not appear that the results from any of the individual centers drive the overall conclusions of the trials. Moreover, the application states that none of the clinical investigators disclose a proprietary interest in the proposed product or significant equity related to the sponsor. Based on this initial analysis, no DSI audit is recommended at this time.</i></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined

<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> ○ <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> 	<p>Reason:</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" 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 checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" 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 checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" 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 checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
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<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" 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 checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" 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 style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" 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 checked="" 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: <i>Applicant will be asked in the 74-day letter to submit a statement indicating that all establishments are ready for inspection.</i></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 checked="" 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>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Badrul A. Chowdhury, Division Director</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>PeRC Mtg: TBA Mid Cycle 8/23/11 TM Labeling 11/8/11 WU 12/13/11 Labeling t-con: TBA Primary Review: 12/28/11 Secondary Review: 1/4/12 Initial Label Due: 1/4/12 CDTL Memo: 1/11/12 DD Memo: 2/1/12 PDUFA Date: 2/1/12</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <p><u>Review Classification:</u></p> <input checked="" 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) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" 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

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.

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

/s/

PHILANTHA M BOWEN
06/14/2011

SANDRA L BARNES
07/15/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202236
Name of Drug: DYMISTA (azelastine/fluticasone) Nasal Spray
Applicant: Meda Pharmaceuticals Inc.
Review Date: May 3, 2011

Labeling Reviewed

Submission Date: April 1, 2011

Receipt Date: April 1, 2011

Background and Summary Description

On April 1, 2011, Meda Pharmaceuticals submitted a 505(b)(2) New Drug Application for azelastine/fluticasone for seasonal allergic rhinitis in patients 12 years of age and older.

The proposed labeling for azelastine/fluticasone was provided in SPL, including electronic carton and container labels.

OSE and DDMAC will be consulted regarding the PI, PPI, PIU as appropriate to their discipline, for recommendations regarding the proposed content.

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. No labeling deficiencies were identified in this section.

However, the following labeling issues were identified:

- All periods following the numbers that precede the section and subsection headings in the Table of Contents and Full Prescribing Information must be omitted. For example,

1. INDICATIONS AND USAGE

(b) (4)

Conclusions/Recommendations

All labeling deficiencies 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. The resubmitted labeling will be used for further labeling discussions.

Selected Requirements for Prescribing Information (SRPI)

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)”

See Appended Electronic Signature

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

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

/s/

PHILANTHA M BOWEN
05/05/2011

SANDRA L BARNES
05/05/2011