CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202236Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

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

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
202236

NAME OF APPLICANT/NDA HOLDER
Meda Pharmaceuticals
Meda Pharmaceuticals Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)
TRADENAME Nasal Spray

ACTIVE INGREDIENT(S)	STRENGTH(S)
azelastine hydrochloride	137 mcg per spray
fluticasone propionate	50 mcg per spray

DOSAGE FORM
Nasal Spray

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

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

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

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

1. GENERAL

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

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

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

PSC Graphics (301) 443-1090 EF

Reference ID: 3127881

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

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

5. No Relevant Patents

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

Reference ID: 3127881

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Richard Fosko	3-16-2011

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

Check applicable box and provide information below.

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

Name Richard Fosko, RPh, MPH, Senior Director Regulatory Affairs, Meda Pharmaceuticals Inc.	
Address 265 Davidson Ave, Suite 300	City/State Somerset, NJ
ZIP Code 08873-4120	Telephone Number 732-564-2358
FAX Number *(if available)* 732-564-2377	E-Mail Address *(if available)* richard.fosko@meda.us

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Reference ID: 3127881

PATENT CERTIFICATIONS

The patent for azelastine hydrochloride in Meda Pharmaceuticals' product ASTELIN® Nasal Spray (NDA 20-114) expires on May 1, 2011.

According to the information in the Food and Drug Administration Orange Book Database (http://www.accessdata.fda.gov/scripts/cder/ob/docs/querytn.cfm), there are no unexpired patents for FLONASE® (fluticasone propionate) Nasal Spray (NDA 20-121, Glaxo Smith Kline).

In accordance with 21 CFR 314.94(a)(12), Meda Pharmaceuticals presents the following certification.

PARAGRAPH II CERTIFICATION:

In accordance with 21 CFR 314.94(a)(12)(i)(2), Meda Pharmaceuticals certifies that, to the best of its knowledge, that the patent for FLONASE® (fluticasone propionate) Nasal Spray expired in May 2004.

Richard Fosko, RPh, MPH
Senior Director, Regulatory Affairs
Meda Pharmaceuticals Inc

3-16-2011
Date

Reference ID: 3127881

EXCLUSIVITY SUMMARY

NDA # **202236** SUPPL # HFD # 570

Trade Name: **Dymista**

Generic Name: azelastine hydrochloride/fluticasone proprionate

Applicant Name: Meda Pharmaceuticals

Approval Date, If Known May 1, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

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

Reference ID: 3124530

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☒ NO ☐

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

No

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA#	20121	Flonase
NDA#	20114	Astelin
NDA#	21433	Flovent HFA

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

Reference ID: 3124530

summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Clinical Trial #1: MP4002
Clinical Trial #2: MP4004
Clinical Trial #3: MP4006
Clinical Trial #4: MP4000

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

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒
Investigation #4	YES ☐	NO ☒

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

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

Investigation #1	YES ☐	NO ☒

Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒
Investigation #4	YES ☐	NO ☒

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

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

Clinical Trial #1: MP4002
Clinical Trial #2: MP4004
Clinical Trial #3: MP4006
Clinical Trial #4: MP4000

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

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

Investigation #1		!
		!
IND # 77363	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 77363	YES ☒	! NO ☐
		! Explain:

Investigation #3		!
		!
IND # 77363	YES ☒	! NO ☐
		! Explain:
Investigation #4		!
		!
	YES ☐	! NO ☒
		! Explain: **conducted outside U.S. (not under IND)**

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

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
Investigation #3	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
Investigation #4	!
	!
YES ☒	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: *Philantha Montgomery Bowen, MPH*
Title: *Sr. Regulatory Management Officer*
Date: *April 11, 2012*

Name of Office/Division Director signing form: *Badrul A. Chowdhury, MD, PhD*
Title: *Division Director*

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

COLETTE C JACKSON
05/01/2012

BADRUL A CHOWDHURY
05/01/2012

3. DEBARMENT CERTIFICATION

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

Veronica Donner
Meda Pharmaceuticals Inc.
Manager, Corporate Quality Assurance

14 MAR 2011
Date

Reference ID: 3127881

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202236 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Dymista Established/Proper Name: azelastine and fluticasone Dosage Form: nasal spray		Applicant: Meda Pharmaceuticals Agent for Applicant (if applicable):
RPM: Philantha Bowen		Division: DPARP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 20121 - Flonase

Provide a brief explanation of how this product is different from the listed drug.

New combination nasal spray

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: May 1, 2012

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is May 1, 2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

Reference ID: 3124552

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): *4*

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☐ MedGuide w/o REMS
- ☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

Reference ID: 3124552

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	5/1/12
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP – 5/1/12
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	4/30/12
• Original applicant-proposed labeling	4/1/11
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

Reference ID: 3124552

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	4/30/12
• Original applicant-proposed labeling	4/1/11
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	4/12/12 (carton), 4/26/12 (container)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Letter: 7/25/11 Reviews: 7/14/11; 4/2/12
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 5/2/11; Labeling mtg 11/8/11 ☒ DMEPA 10/31/11 ☒ DMPP/PLT (DRISK) 11/22/11 ☒ ODPD (DDMAC) 11/25/11 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	7/15/11 ☐ Not a (b)(2) 3/30/12 ☐ Not a (b)(2) 5/1/12
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 3-21-12 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	4/8/11, 6/13/11, 8/31/11,9/13/11, 9/15/11, 9/23/11, 10/4/11, 10/21/11, 11/17/11, 11/21/11, 3/19/12, 3/30/12, 4/24/12,
❖ Internal memoranda, telecons, etc.	13/13/11, 2/16/12
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg 4/17/09
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 8/17/10
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	SPA – 4/29/08; Guidance 9/10/07; 6/25/07
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 5/1/12
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 4/10/12
PMR/PMC Development Templates *(indicate total number)*	☐ None 4/30/12
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL review
• Clinical review(s) *(indicate date for each review)*	5/31/11, 3/27/12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	3/27/12, page 16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None *See concurrence on primary review*
Statistical Review(s) *(indicate date for each review)*	☐ None 5/24/11, 12/28/11
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None *See concurrence on primary review*
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 5/20/11, 12/22/11
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 12/7/11
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 5/13/11, 9/23/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Reference ID: 3124552

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 4/5/12
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 5/28/11; 3/27/12
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 1/12/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None Nonclinical - 9/23/11
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	3/27/12, page 141
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 4/30/2012 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review) 3/27/12, page 8

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Reference ID: 3124552

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

Reference ID: 3124552

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/s/

COLETTE C JACKSON
05/01/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: April 27, 2012

To: Brenda Jadney

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 (Dymista) - Labeling Recommendations Request (#4)

# of Pages including cover:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Your submission dated April 26, 2012, regarding the labeling to NDA 202236, is currently under review. In the attached label, the FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we will have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the label by 9 am Monday, April 30, 2012, to the NDA. In addition, please forward a courtesy copy via email to Ms. Colette Jackson at colette.jackson@fda.hhs.gov.

If you have any questions, contact Ms. Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

{See appended electronic signature page}

_____

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

Reference ID: 3123559

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/s/

COLETTE C JACKSON
04/27/2012

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: April 20, 2012

To: Brenda Jadney

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 (Dymista) - Labeling Recommendations Request (#3)

# of Pages including cover: 41

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Thank you.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Your submissions dated July 1, 2011, and February 27, March 23, and April 4, 2012, regarding the labeling to NDA 202236, are currently under review. In the attached label, the FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we will have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the label by COB Wednesday, April 25, 2012, to the NDA. In addition, please forward a courtesy copy via email to Ms. Colette Jackson at colette.jackson@fda.hhs.gov.

If you have any questions, contact Ms. Jackson, Sr. Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

{See appended electronic signature page}

_____

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

COLETTE C JACKSON
04/24/2012

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: March 30, 2012

To: Brenda Jadney

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 (Dymista) - Labeling Recommendations Request (#2)

# of Pages including cover: 43

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If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Your submissions dated July 1, 2011, and February 27 and March 23, 2012, regarding the labeling to NDA 202236, are currently under review. Submit revised draft labeling incorporating our recommendations noted below as well as those in the attached document. In the attached label, the FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we will have additional recommendations as we continue our review of the label. Submit a clean copy and a tracked-change version of the label by Tuesday, April 3, 2012, to the NDA. In addition, please forward a courtesy copy to me via email.

A. The following pertains to the Package Insert Labeling

1. Section 14 Clinical Studies
   Trials MP 4002 and MP 4004 were selected for presentation as they provide robust, replicated evidence of the factorial contribution of each component. The analysis based on raw data for 4006 was supportive, but not as consistently robust.

2. Section 17 Patient Counseling Information
   (b) (4)

B. The following pertain to the Patient Information and Instructions for Use (IFU) Labeling

1. Section "How should I use DYMISTA Nasal Spray?"
   (b) (4)
2. Locate related text directly above, below, or beside the appropriate figure referenced.
3. Provide a detailed image of the device in Figure A and clearly identify the device with the same names that are used in the steps of the IFU. These include: dust cap, spray pump tip, shoulders of the spray pump, spray pump unit, and bottle.
4. Include a Figure B where indicated to show the cap being removed.
5. Include a Figure D where indicated to describe Step 3.
6. Include a Figure E where indicated. It should be similar to Figure F, but with "a finger over other nostril" as described in Step 4.
7. Include a Figure G where indicated corresponding to Step 6.
8. Include a Figure H where indicated describing Step 7.
9. Add the month/year to the last line of the document.

C. The following pertains to the Carton Label (6 g, Sample Size and 23 g, Trade Size)

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

2. Change the statement [redacted] (b) (4) to "Discard after 28 actuations" on the 6 g Carton Label.

3. Decrease the prominence of the phrases "6 g" or "23 g" by decreasing font size and eliminating bright blue circle around them as these statements are as prominent as the strength of the product.

4. [redacted] (b) (4)
   Thus, revise the background color or the color and font size of the text to ensure adequate prominence of the route of administration.

5. Improve the prominence of the nonproprietary part of drug product name.

6. Replace the fill weight on the front panel (white print on blue circular background) with the number of metered sprays, i.e., 120 Metered Sprays for trade carton, and 28 Metered Sprays for sample carton.

7. Improve the legibility (e.g., change color, font, font size, as needed) of the front panel information provided [redacted] (b) (4)

8. Revise the storage recommendations to read:

   > Store upright, with dust cover in place, at controlled room temperature 20ºC-25ºC (68º-77ºC).
   > Protect from light. Do not store in the freezer or refrigerator.
   > Keep away from children.

D. The following pertains to the Container Label (6 g, Sample Size and 23 g, Trade Size)

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

2. Add a statement "Delivers 28 Metered Sprays" to the 6 g Container Label.

3. 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.

4. Reconcile the storage information with revisions recommended for the carton labels.

If you have any questions, contact me at 301-796-2466.

Enclosure: Package Insert
Patient Package Insert
Carton/Container Labels

Sincerely,

{See appended electronic signature page}

_____
Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Drafted: Bowen/3-29-12

Clearance: Robison/3-30-12
Wood/3-30-12
Jafari/3-30-12
Jain/3-30-12
Pippins/3-30-12
Limb/3-30-12
Shang for Doddapaneni/3-30-12
Peri/3-30-12

Finalized: Bowen/3-30-12

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

Reference ID: 3109901

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/s/

PHILANTHA M BOWEN
03/30/2012

Bowen, Philantha

'om:	Greeley, George
nt:	Tuesday, March 27, 2012 5:48 PM
'o:	Bowen, Philantha
Cc:	Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Chowdhury, Badrul A; Pippins, Jennifer R.
Subject:	NDA 202-236 Dymista
Importance:	High
Attachments:	1_Pediatric_Record.pdf

Hi Philantha,

The email serves as confirmation of the review for Dymista (Azelastine/Fluticasone) aerosol product conducted by the PeRC PREA Subcommittee on January 25, 2012.

Dymista is a combination product seeking approval for use in adolescents 12 years of age and older. At an earlier discussion held on November 30, 2011 the PeRC agreed to a waiver in patients less than 2 years of age because the disease/condition does not exist and to a waiver in patients 2 to <4 years where the combination is unlikely to be used because it does not offer a meaningful therapeutic benefit.

The Division presented a partial waiver for patients ages birth to 23 months because studies would be impossible or highly impracticable because the diagnosis is uncertain in this age group and a partial waiver in patients 2-3 years because the product does not represent a meaningful therapeutic benefit. A deferral was presented for patients 4-11 years because the product is ready for approval in adults and an assessment for those patients 12-16 years of age for the indication of treatment of nasal (b) (4) symptoms associated with seasonal allergic rhinitis in patients 12 years of age and older.

The PeRC agreed with the Division to grant a partial waiver, deferral and assessment.

The pediatric record is attached for Dymista.

1_Pediatric_Record .pdf (66 KB)...

Thanks,

George Greeley
Senior Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

Please consider the environment before printing this e-mail.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: March 19, 2012

To: Brenda Jadney, Associate Director
Regulatory Affairs

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 - CMC Information Request

# of Pages including cover: 5

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Thank you.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Reference is made to your NDA submission dated April 1, 2011, which is currently under review and we have the following CMC comments and requests for information.

We also refer to your submission dated December 7, 2011, provided in response to the Agency's information request facsimile dated November 17, 2011. We note you have not fully addressed our comments dated November 17, 2011. We are requesting additional information and reiterating some of our previous requests regarding Comments 4, 5, 5c, 5d, 5e, 5f, 5g, 5i, 5j, 5k, and 7, as listed in the November 17, 2011, facsimile. The outstanding deficiencies to address are listed in bold font.

Regarding Comment 4 of our facsimile dated November 17, 2011:

1. **Submit complete acceptance specifications for** (b) (4) **with list of tested attributes, numbers for corresponding analytical methods and acceptance criteria, including acceptance criteria for particle size distribution. Based on data submitted for the clinical and registration batches, the following acceptance criteria seem to be justified:** (b) (4) **Provide the Certificate of Analysis (COA) for a representative** (b) (4) **batch to be used in the to-be-marketed product.** (b) (4)

Regarding Comments 5, 5c, 5d, 5e, 5f, 5g, 5i, 5j, 5k of our facsimile dated November 17, 2011:

2. **Submit final regulatory specifications for the release and stability testing of the drug product intended for marketing. The drug product specifications submitted on December 7, 2011, indicate testing on release only. Note that the EDTA ingredient should be tested at release and during stability.** (b) (4) **the proposed acceptance criteria for the content of individual and total impurities and for the viscosity and weight loss of the drug product, to reflect the submitted stability data, since these attributes are stability-indicating factors for evaluation of the drug product expiry. In addition, include the previously requested revisions, as follows:**

   a. **PUMP SPRAY WEIGHT: Revise the method and the proposed acceptance criteria for Pump Spray Weight to include the weight of the**

Reference ID: 3103579

delivered drug product suspension at the beginning and at the end of the container (pump) life. Define [redacted] and include the acceptance criteria for the mean spray weight [redacted]

b. DROPLET SIZE DISTRIBUTION: Revise the analytical method and [redacted] the proposed acceptance criteria to reflect the results obtained for the representative to be marketed drug product batches. Define [redacted]) and include the acceptance criteria for the D_{10}, D_{50} and D_{90} [redacted]

c. SPRAY PATTERN: We reiterate our comment to revise the method and proposed acceptance criteria. Revise acceptance criteria for Shape to read: [redacted] The proposed controls for mean D_{max} and mean ovality ratio have to be reflective of test results. The results included in the calculation of mean value should be based on [redacted]

d. PARTICLE SIZE DISTRIBUTION: Propose data-based acceptance criteria for three non-overlapping regions of the distribution curve e.g., below 2.5 µm, between 2.5 µm and 5 µm, and between 5 µm and 10 µm.

e. SPRAY CONTENT UNIFORMITY: Revise the specifications and description of calculations in the analytical method [redacted]

f. CONTENT OF PHENYLETHYL ALCOHOL (PEA): [redacted] the shelf-life acceptance criteria for the content of PEA to [redacted] for the trade product and to [redacted], for the physician sample product.

[redacted]

(b) (4)

Regarding Comment 7 of our facsimile dated November 17, 2011:

3. **DRUG PRODUCT EXPIRY: (b) (4) the proposed expiry period to (b) (4) 24 months, (b) (4)**

(b) (4)

Submit the finalized analytical methods and specifications, as requested above, to support the proposed expiry period.

Submit an official response to the NDA by March 22, 2012, or sooner if possible. If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Nashed/03-16-12

Clearance: Jafari/3-19-12
Peri/3-19-12
Nashed/3-19-12

Finalized: Bowen/3-19-12

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/s/

PHILANTHA M BOWEN
03/19/2012

MEMORANDUM

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

DATE: February 16, 2012

TO: NDA 202236 - File

THROUGH: Prasad Peri, Ph.D., Branch Chief
Eugenia Nashed, Ph.D., CMC Reviewer

FROM: Philantha Bowen, MPH, Sr. Regulatory Project Management Officer

SUBJECT: Memorandum to File: Meeting Minutes for November 22, 2011

APPLICATION/DRUG: Dymista (azelastine hydrochloride/fluticasone propionate) Nasal Spray, 137/50 µg per spray

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TELECON DATE: November 22, 2011
TIME: 12:00 – 12:45 PM EST
LOCATION: Teleconference
TYPE OF MEETING: CMC only
MEETING CHAIR: Prasad Peri, Ph.D., Branch Chief
MEETING RECORDER: Philantha Bowen, MPH, Sr. Regulatory Project Management Officer

FDA ATTENDEES:

ONDQA, Division of Pre-Marketing Assessment III, Branch VIII

Prasad Peri, Ph.D., Branch Chief
Alan Schroeder, Ph.D., CMC Lead
Eugenia Nashed, Ph.D., CMC Reviewer

Office of Drug Evaluation II, Division of Pulmonary, Allergy, and Rheumatology Drug Products

Philantha Bowen, M.P.H., RN, Sr. Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Meda Pharmaceuticals

Francis Barbone, PhD, Senior Director Regulatory Affairs
Mary Lehr, Manager Technical Services,
Cindy Yayac, Senior Manager Regulatory Affairs

BACKGROUND:

ONDQA granted a teleconference with Meda to clarify the CMC IR dated November 17, 2011.

MEETING OBJECTIVES:

The purpose this teleconference is to convey to Meda the current status of the application in terms of timeline and review progress of the CMC information. Additionally, the objective of this meeting to clarify and/or further explain the CMC requests outlined in the IR dated November 17, 2011.

DISCUSSION POINTS:

In an email correspondence dated November 21, 2011, Meda requested that the Division provide additional clarity regarding for items 5 and 6 outlined in the CMC IR facsimile dated November 17, 2011. Below is Meda's request for clarity and response to the CMC IR:

Request for clarity regarding Request for CMC/Micro Information dated November 17, 2011.

5. Submit revised regulatory specifications for the release and stability testing of the drug product intended for marketing.

- Specify the laboratory/party responsible for each test and indicate with footnotes which attributes are tested for release or stability only.

  The analytical testing site was identified in 3.2.P.3.1 (Manufacturer) as defined in the CTD structure. The analytical test site is:

  Cipla Ltd.
  Plot No. L139 to L146
  Verna Industrial Estate

Verna, Salcette 403722
Goa, India

The attributes tested for release and stability were provided in 3.2.P.5.1 (Specifications) as separate tables:

Bulk Release:	*Table 1*
Packaged Product Release:	*Table 2*
Stability:	*Table 3*

In addition, a combined comparative table (Table 4), as requested by the CMC Reviewer in the 74-day letter, was also provided. Table 4 has column headers identifying the specifications/tests for each category (Bulk Release, Packaged Product Release, and Stability). Please note that in Table 4 where a test is not required for release or stability it is designated by "N/A". We believe the information already provided has addressed this request.

- Attach a sheet with the names and structures of all identified impurities.

  The names and structures of all identified impurities in the finished product were provided in Section (3.2.P.5.5), Tables 1 and 2 (pages 3 and 4).

  We believe that this request has already been addressed in the original submission.

Provide the specification number, date, and include the following revisions.

6. Resubmit the stability data for the representative to-be-marketed drug product batches to include individual numerical data for each attribute instead of providing data ranges, "meets the requirements" statement, <LOD, < LOQ, and ND or N/A abbreviations. Provide the mean values (based on validated analytical method which was used for testing) and report the actual LOD and LOQ numbers validated for the given analytical method. Include statement "Not tested" if the test was not performed. Provide statistical evaluation of trends with confidence intervals and graphic charts for stability-indicating attributes, like the Spray Content Uniformity, Weight Loss, Droplet Size Distribution, Particle Size Distribution, Impurities, pH, and Content of phenylethyl alcohol.

   In section 3.2.P.8.3 "Stability - Trade Pack - Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray", Section 3.2 is a table identifying all abbreviations used in the stability tables. Section 3.3 Table 2, lists the values of all Limits of Detection and Quantification reported in the stability tables. The same information was also provided in the Stability Data for the Sample pack. In addition, in Section 3.2.P.8.1, all data tables having such a limit were included as footnotes in the individual tables. We believe the information already provided has addressed this portion of the request.

   In regards to the request to submit statistical evaluation of trends with confidence

intervals, these graphs were submitted with trend lines and confidence intervals on September 23, 2011 in Sequence 0008, in Section 3.2.P.8.3 (Stability Graphs). We believe the information already provided has addressed this portion of the request.

Discussion on Response 5:

Meda began the discussion by summarizing their comment outlined above. Meda stated that the manufacturing sections of the application have testing information and that there are no additional testing sites in connection with the specifications. Moreover, the tabular formats requested for release/stability data, as well as, a comparator table have been previously submitted. The FDA clarified that one table with regulatory specifications is needed, to include individual method numbers, revised attributes, and acceptance criteria as requested in Comment 5 a-l, of the November 17, 2011, information request. The document needs to be signed by an official responsible for the release of the product and for the product lifetime adherence to the specifications. The FDA stated, that the deficiency can be addressed effectively by providing one table containing the bulk release information, and followed by the release and stability information outlined together. Currently, four tables have been submitted without specification numbers, signatures, and effective dates. For regulatory purposes, drug products must have clear and accountable specifications, thus Meda needs to revise the format of the product specifications, include the requested revisions and submit the final document for review.

Since the document would be considered a draft, Meda proposed to provide the specifications in the revised format, then submit the signed specifications document subsequently after FDA's concurrence. The FDA recommended that Meda provide one table, containing each specification number, effective date, and name of the responsible official and with all the requested revisions. In addition, following the table, Meda will need to include a page listing chemical names and structural formulas for all identified impurities. Meda responded that the impurity and structure information has been previously submitted. The FDA acknowledged submission of this information, but explained that the requested impurity, chemical name, and structure information should coincide with the abbreviated names and data presented in the specifications table and may be provided as an attachment to the specifications table.

Discussion on Response 6:

Meda stated that the requested LOD, LOQ, etc. listing has been previously submitted to the NDA and is located at the beginning of the stability data. The FDA acknowledged that the following information has been submitted to the NDA: 1) original stability data; 2) summaries and conclusions; 3) graphs without evaluations; and 4) comparisons with monotherapies. Meda agreed. The FDA explained that the graphs for pH, weight loss, droplet size distribution, and mean spray compound currently under review, do not contain data for particle size distribution. Meda only provided data ranges without any mean values for the requested items. The FDA requested that Meda re-submit the data since the correct specifications need to be established. Meda commented that the graphs contained proposed specifications and asked if they could provide a rationale, without additional analysis, if the specifications are acceptable and no change is observed. The FDA responded that Meda will need to conduct an analysis of the

stability data in support of the proposed acceptance criteria. Meda needs to provide complete results, with individual measurements and mean values and with out-of-trend results identified. Providing a data range only is not acceptable.

Meda commented they are currently working to obtain individualized information and could provide the other data as separate tables. The FDA stated that Meda needs to respond to all requests in item 5 of the IR since this will impact stability data. In response to a question about the extent of the stability data to be summarized, FDA indicated that Meda may select three representative batches. Meda proposed to provide particle size distribution in a separate table, then submit an updated table once all information is obtained. The FDA stated that stability data are needed for evaluation of proposed specifications and need to be submitted for review, along with appropriate statistical evaluation The FDA explained that Meda will need to provide particle size distribution, etc., and include the number of sprays. The FDA noted that the number of sprays per container is part of the labeling and also needs to be in the specifications. The content uniformity method may be revised to determine the number of sprays per container. The FDA reiterated that one report table should be provided that includes regulatory attributes, analytical methods, release and stability acceptance criteria , and data for all attributes of the tested batches, including the mean values, as requested. Meda asked if it was acceptable to provide one stability table for one representative batch and if only updated specifications could be provided, and then provide the manufacturing batch data at a later time. The FDA did not agree. The FDA stated that Meda needs to submit data from at least one representative stability batch (most recent) in the requested revised format. The FDA explained that data report format has to correspond to the specifications format and has to be determined during the NDA review. Furthermore, the FDA commented (in response to Meda's request) that Meda may not provide a blank template with specification information without any data. Meda needs to submit at least one representative stability batch with all requested attributes and data.

In terms of responding to the CMC IR, the FDA asked Meda to provide their timeframe for submitting the specifications with one upright batch along with a full complete response to the IR. Meda requested an extension date of December 7, 2011. The FDA agreed to the revised date for submission of a complete response to the IR.

DECISIONS (AGREEMENTS) REACHED:

- For regulatory specifications, Meda will provide one table in final format. Omission of official signatures is acceptable at this time, however the name(s) should be provided. Impurity, chemical name, and structure information should coincide with the abbreviations and data presented in the specifications table and may be provided as an attachment to the specifications table.

- Meda will need to submit particle size distribution data and mean values for the requests outlined in the November 17, 2011, IR for #5 (a-l).

- Meda will need to conduct and submit an analysis of stability data for specifications outside of the trend since no mean particle size distribution was provided.

- Meda needs to submit data for at least one representative batch with all requested attributes and data in the format outlined.

- FDA agreed to submission of complete response by December 7, 2011

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

No issues requiring further discussion noted at this time.

ACTION ITEMS:

- Meda to provide a complete response to pending Microbiology and CMC information requests in one submission.

_____

Philantha Montgomery Bowen, M.P.H., RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PHILANTHA M BOWEN
02/16/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202236

REVIEW EXTENSION – MAJOR AMENDMENT

Meda Pharmaceuticals, Inc.
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Brenda Jadney, B.A.
Associate Director, Regulatory Affairs

Dear Ms. Jadney:

Please refer to your April 1, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dymista (azelastine/fluticasone) Nasal Spray, 137 µg/50 µg (0.1%/0.037%).

On December 7, 2011, we received your December 7, 2011, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 1, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 10, 2012.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
12/13/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: November 21, 2011

To: Brenda Jadney

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 (Dymista) - Labeling Recommendations

# of Pages including cover : 42

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Thank you.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

We have begun our review of the labeling in your submission dated July 1, 2011, to NDA 202236. The FDA-proposed insertions are underlined and deletions are in strike-out. We have the following comments and/or requests for revisions pertaining to the labeling:

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

    a. Add instructions regarding what steps should be taken if the product is accidentally sprayed in the eyes.

    b. Incorporate labeling, if necessary, addressing the limitations of device ruggedness (as discussed during the October 11, 2011, post-midcycle teleconference). Provide justification if you choose not to incorporate additional instructions into the label.

3. Section 6.1 Clinical Trials Experience

    a. The safety data have been revised to reflect the findings of the three clinical trials which used the appropriate comparators, not the commercial monoproducts.

    b. Add a footnote to Table 1 explaining the discrepancy between the size of the safety population (n=853) and the intent to treat population (n=848).

4. Section 17 Patient Counseling Information

    a. Add labeling addressing HPA axis effects.

    b. Add labeling addressing potential growth effects.

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 instructions regarding what steps should be taken if the product is accidentally sprayed in the eyes.

c. Incorporate labeling, if necessary, addressing the limitations of device ruggedness (as discussed during the October 11, 2011, post-midcycle teleconference). Provide justification if you choose not to incorporate additional instructions into the label.

2. Revise the label to 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. Add illustrations to Section *To Clean the Spray Tip* to aid consumer understanding of the cleaning instructions.

4. 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)]

C. Carton 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)] 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]

5. [redacted] Additionally, this [redacted] 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]
8. Add the statement "Shake the bottle gently before each use" to the principle display panel.
9. [redacted] We request you delete [redacted]
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] to read "Initial priming: 6 sprays or until a fine mist appears". Additionally, revise the statement [redacted] 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 addition 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.

17. The front panel should be less crowded and contain the following information:

    a. Clearly legible full name of the drug product with content per spray. Increase the the size and prominence of the non-proprietary name, e.g.,

    Dymista
    (azelastine hydrochloride/
    fluticasone propionate)
    Nasal Spray
    137 mcg/50 mcg (0.1%/0.037%)
    per spray

    b. Clearly legible and prominent administration route information " **For Intranasal Use Only**".

    c. "**Rx only**" information.

    d. "**120 Metered Sprays**" information.

    e. "**23 g net fill weight**" information.

    f. NDC number

18. The side panel #1 should include composition information and storage conditions, in addition to the full name and spray content, e.g.,

    Contents: An aqueous suspension containing azelastine hydrochloride, fluticasone propionate, 0.01% benzalkonium chloride,… pH approximately 6.

    Usual Dosage: See prescribing information.

    Store upright between 20°C and 25°C (68°F -77°F).

    Protect from freezing and light.

19. The side panel #2 should include Dosing Instructions, e.g.,

    Important: Read accompanying directions leaflet carefully.

Shake gently before each use.

Discard after 120 actuations.

Drawings 1, 2 and 3 with brief instructions.

20. The back panel should contain full name of the drug product with content per spray, as on the front panel, and the names and addresses of the manufacturer and the distributor. Change the name Meda from all capital case to the title case letters and increase the size and prominence of the name of the manufacturer.

D. 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. (b) (4) Thus, revise the presentation of the strength (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 (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)
13. Revise the container label to coincide with the revised carton label. Due to the limited space remove the [redacted] (b) (4) [redacted] (b) (4) and [redacted] (b) (4) to improve the legibility of the label.

Be advised that these comments are not all-inclusive and we will have additional recommendations as we continue our review of the label. We do not expect you to provide revised labeling at this time. When requested, you will need to submit paper copies of the mockup revised labels for carton and immediate container. However, if you have questions regarding any of the recommendations, we request that you forward your comments so that we may address any issues you may have.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

If you have any questions, contact me at 301-796-2466.

Enclosure: Package Insert
Patient Instructions for Use

Sincerely,

{See appended electronic signature page}

_____

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Drafted: Bowen/11-15-11

Clearance: Zhou/11-16-11
Robison/11-16-11
Wood/11-16-11
Jafari/11-15-11
Jain/11-15-11
Pippins/11-16-11
Limb/11-16-11
Doddapaneni/11-17-11
Peri/11-18-11

Finalized: Bowen/11-21-11

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

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/s/

PHILANTHA M BOWEN
11/21/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: November 17, 2011

To: Brenda Jadney, Associate Director
Regulatory Affairs

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 Re: Microbiology/Quality Information Request

# of Pages including cover: 8

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Thank you.

Reference ID: 3046284

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Your NDA submission dated April 1, 2011, is currently under review and we have the following Microbiology and CMC comments and requests for information:

1. We remind you of pending requests to submit the following information and data.

    a. Revisions for the microbiological controls of drug product (validated method and acceptance criteria for the presence of *B. cepacia*), as described in our correspondence dated August 31 and September 13, 2011.

    b. Address the lack of ruggedness for the container closure system by implementing necessary changes and submitting data demonstrating no changes in the dose performance. This was discussed during the teleconferences on September 1 and October 11, 2011.

    We request that you submit the responses to the above issues together with the response to the additional comments listed below, in a single amendment to the NDA.

Microbiology

2. Your proposed commercial product stability testing protocol should be amended to include a microbial limits *Burkholderia cepacia* detection assay and acceptance criterion.

CMC

3. Provide particle size distribution data for the clinical and registration batches, for both release and stability testing. This was requested in the Agency letter dated June 13, 2011, and discussed during subsequent teleconferences and communications on July 19, 20 and 22, 2011. Include individual results and mean values (with the data range and/or standard deviation) for each batch, instead of providing the data range only. Also, submit comparative summary graphs for means of particle fractions below 2.5 µm, for the clinical combination batches G70453, G70454, G70455, G70456 and G90758. In addition, provide two comparison graphs for the same data (mean for particles ≤ 2.5 µm) addressing the comparability of the combination drug products used in clinical trials to the corresponding monocomparator drug products, i.e., batches G70453 and G70454 *versus* G71092, and batch G90758 *versus* G90767. Explain (b) (4) in comparison to the other clinical and stability batches.

Reference ID: 3046284

4. Provide specifications for the excipient [redacted] for particle size distribution to assure continuous quality and dose performance of the drug product. Include supporting data from the [redacted] acceptance testing for lots utilized in the manufacturing of the drug product registration batches. Alternatively, demonstrate that changes in the particle size distribution of the [redacted] component (which may happen) do not change the quality characteristics and dose performance of the drug product.

5. Submit revised regulatory specifications for the release and stability testing of the drug product intended for marketing. Specify the laboratory/party responsible for each test and indicate with footnotes which attributes are tested for release or stability only. Attach a sheet with the names and structures of all identified impurities. Provide the specification number, date, and include the following revisions.

   a. Acceptance criteria and a validated method for Number of Sprays (e.g., NLT 120), containing amounts of APIs equivalent to the label claim.

   b. Revised acceptance criteria for pH [redacted]

   c. A revised acceptance criteria for Pump Spray Weight by describing how results are obtained. [redacted] Also, revise and resubmit the currently proposed method AM 003-FGNA012V5 [redacted]

   e. Revised acceptance criteria and a modified method for the Droplet Size Distribution. Describe how results are obtained and [redacted] the proposed acceptance criteria to reflect the data. Include acceptable ranges for the means

for D_{10}, D_{50} and D_{90}. Also, (b) (4) the proposed acceptance criteria for the mean span of the spray, based on available data. Refer to the example below.

Test	Acceptance Criteria	Analytical Method
Droplet size distribution by laser diffraction Mean D_{10} (µm) Mean D_{50} (µm) Mean D_{90} (µm) Mean droplets <10 µm (%) Mean span [$(D_{90}$-$D_{10})/D_{50}$]	(b) (4)	AM 004-FGNA012V5 (version x)

f. Revised acceptance criteria and a modified method for the Spray Pattern to include a description of how the results are obtaine (b) (4)

Mean longest axis [D_{max} (mm)] Mean ovality ratio Mean inclusion ratio	(b) (4)

Provide supporting release and stability data for the spray pattern to justify the proposed acceptance criteria.

g. Revised acceptance criteria and a modified method for Particle Size Distribution by microscopy to include (in addition to the screening for agglomeration, crystal growth, etc.) the description of how the results are obtained, similarly to the droplet size distribution attribute, above. Include the acceptance values for the mean percentage of particles in each fraction, e.g.,

Mean % particles ≤ 2.5 µm Mean % particles ≤ 5 µm and ≥ 2.5 µm Mean % particles ≤ 10 µm and ≥ 5 µm	(b) (4)

Provide supporting release and stability data for the particle size distribution of the to-be-marketed batches to justify the proposed acceptance criteria.

h. Revised acceptance criteria for the Foreign Particulate Matter by providing the actual size ranges for particle screening, rather than a general description only (Current description: under microscope, under magnifying glass), e.g.,

(b) (4)

i. Revised acceptance criteria for the Spray Content Uniformity for azelastine hydrochloride and fluticasone propionate to include numeric values of the acceptance criteria for separate mean doses delivered from the beginning and end of the container, and followed by the 2nd tier testing descriptions. Refer to the example below.

Test	Acceptance Criteria	Analytical Method
Spray Content Uniformity of Fluticasone propionate by HPLC through container life (µg/spray)	(b) (4)	AM 007-FGNA012V (version x)
Mean dose delivered from beginnir of container (µg/spray)		
Mean dose delivered from end of container (µg/spray)		
Label Claim (µg/spray)		
Individual dose delivered (µg/spray		

(b) (4)

j. (b) (4) acceptance criteria for individual and total impurities based on the available release and stability data for the to-be-marketed drug product batches.

(b) (4)

l. Revised controls for Microbial limits with (b) (4) acceptance criteria for total aerobic count to reflect the data, and with a new method and acceptance criteria for the presence of *B. cepacia*, as requested in our letter dated August 31, and September 13, 2011.

6. Resubmit the stability data for the representative to-be-marketed drug product batches to include individual numerical data for each attribute instead of providing data ranges, "meets the requirements" statement, <LOD, < LOQ, and ND or N/A abbreviations. Provide the mean values (based on validated analytical method which was used for testing) and report the actual LOD and LOQ numbers validated for the given analytical method. Include statement "Not tested" if the test was not performed. Provide statistical evaluation of trends with confidence intervals and graphic charts for stability-indicating attributes, like the Spray Content Uniformity, Weight Loss, Droplet Size Distribution, Particle Size Distribution, Impurities, pH, and Content of phenylethyl alcohol.

7. Reevaluate and resubmit your proposal for the drug product expiry. The currently proposed (b) (4) expiry period is not adequately supported by the submitted data, with out-of-trend instability changes noted for impurities, weight loss, particle size distribution and content of the phenylethyl alcohol. Resubmit the supporting data in the revised format, as requested above, and provide statistical evaluation of the observed changes.

Submit an official response to the NDA by November 30, 2011, or sooner if possible. If you have any questions, contact Philantha Bowen, Senior Regulatory Project Management Officer, at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/11-15-11

Clearance: Jafari/11-15-11
Peri/11-16-11
Metcalfe/11-17-11
Fong/11-17-11
Nashed/11-16-11

Finalized: Bowen/11-17-11

Reference ID: 3046284

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/s/

PHILANTHA M BOWEN
11/17/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: October 21, 2011

To: Brenda Jadney, Associate Director
Regulatory Affairs

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 Re: Clinical Information Request

# of Pages including cover: 4

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Thank you.

Your submission dated October 18, 2011, to NDA 202236 is currently under review. We note that the Table A provided in this submission was for the Safety Population, and not the ITT population, as requested in our information request dated October 4, 2011. We have the following request for information:

Resubmit the following table, for the ITT population, omitting all data for Trial MP-4001 from this table. Note that the columns entitled "azelastine hydrochloride" and "fluticasone propionate" refer to the investigational monotherapy comparators evaluated in Trials MP-4002, MP-4004, and MP-4006.

Table A. Demographics and Baseline Characteristics for the pooled ITT population, Trials MP-4002, MP-4004, and MP-4006

Category	MP29-02 N=	Placebo N=	Azelastine hydrochloride N=	Fluticasone propionate N=
Age (Years)				
Mean (SD)				
Median				
Min-Max				
12 to < 18				
18 to < 65				
65 or older				
Sex [n(%)]				
Male				
Female				
Race [n(%)]				
White				
Black				
Asian				
Native Hawaiian or other Pacific Islander				
American Indian or Alaska Native				
Other				
Height (inches)				
N				
Mean (SD)				
Median				
Min-Max				

Weight (lb)				
N				
Mean (SD)				
Median				
Min-Max				
Total rTNSS Score[b]				
Mean (SD)				
Median				
Min-Max				
Duration of SAR History (Years)				
Mean (SD)				
Median				
Min-Max				

Submit an official response to the NDA by October 28, 2011, or sooner if possible. If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted by: Bowen/10-20-11

Initialed by: Jafari/10-20-11

Finalized by: Bowen/10-21-11

Reference ID: 3032419

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/s/

PHILANTHA M BOWEN
10/21/2011

MEMORANDUM

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

DATE: October 11, 2011

TO: NDA 202236

FROM: Angela Ramsey
Senior Regulatory Project Manager

SUBJECT: Post- Midcycle teleconference

APPLICATION/DRUG: NDA 202236/Dymista (azelastine/fluticasone)

The Division had a post- midcycle teleconference with Meda Pharmaceuticals on October 11, 2011, to discuss and provide an update on outstanding issues with the NDA review.

1. The Division stated that the CMC review of the dose performance comparison of the monocomponent drug products to the combination drug product (Amendment dated September 24, 2011) is pending and thus may impact the interpretation of the clinical data.

2. The Division stated concerns with the lack of ruggedness of the proposed nasal spray device. The Division reported while removing the dust cover, the nasal actuator separated from the device (all samples submitted to the Division) exposing the pump. Repeated actuation is causing leakage of the drug product formulation from the device.

Meda Pharmaceuticals has discussed these issues with the manufacturer and vendor of the pump and has identified some potential issues requiring modifications to the container closure system; which Meda believes may be the source of the problem. Meda anticipates changes to the container closure within 3-5 weeks and will provide the Division with the adjustments and data by late this year or early next year.

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/s/

ANGELA H RAMSEY
10/13/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: October 4, 2011

To: Brenda Jadney, Associate Director
Regulatory Affairs

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 Re: Clinical Information Request

# of Pages including cover: 7

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Thank you.

Your submission dated April 1, 2011, to NDA 202236 is currently under review and we have the following clinical comment and request for information:

Resubmit the following tables omitting all data for Trial MP-4001 from these tables. Note that the columns entitled "azelastine hydrochloride" and "fluticasone proprionate" refer to the investigational monotherapy comparators evaluated in Trials MP-4002, MP-4002, MP-4004, and MP-4006.

Table A. Demographics and Baseline Characteristics for the pooled ITT population, Trials MP-4002, MP-4004, and MP-4006

Category	MP29-02 N=	Placebo N=	Azelastine hydrochloride N=	Fluticasone propionate N=
Age (Years)				
Mean (SD)				
Median				
Min-Max				
12 to < 18				
18 to < 65				
65 or older				
Sex [n(%)]				
Male				
Female				
Race [n(%)]				
White				
Black				
Asian				
Native Hawaiian or other Pacific Islander				
American Indian or Alaska Native				
Other				
Height (inches)				
N				
Mean (SD)				
Median				
Min-Max				
Weight (lb)				
N				

Mean (SD)				
Median				
Min-Max				
Total rTNSS Score[b]				
Mean (SD)				
Median				
Min-Max				
Duration of SAR History (Years)				
Mean (SD)				
Median				
Min-Max				

Table B. Disposition of Subjects in the pooled ITT population, Trials MP-4002, MP-4004, and MP-4006

Disposition	MP29-02	Placebo	Azelastine hydrochloride	Fluticasone propionate
All Randomized Subjects (N)				
Number of Subjects who Completed, n (%)				
Number of Subjects who Discontinued, n(%)				
Primary Reason for Discontinuation, n (%)				
Adverse Event				
Abnormal Test Result				
Treatment Failure				
Protocol Violation				
Noncompliance				
Subject Withdrew Consent				
Lost to Follow- up				
Administrative Problem				
Other				
Safety Population[a], n (%)				
ITT Population[b], n (%)				
PP Population[c], n (%)				

Table C. Duration of Exposure and Compliance, Safety Population: Trials MP-4002, MP-4004, MP-4006

	MP29-02 N=	Placebo N=	Azelastine Hydrochloride N=	Fluticasone Propionate N=
Duration of Exposure (Days)				
Mean (SD)				
Median				
Min-Max				
Total No. of Doses Taken				
Mean (SD)				
Median				
Min-Max				
Subjects Treatment Compliant[#]:				
Day 7 [n(%)]				
Day 14 [n(%)]				
Subjects with ≥ 80% Compliance [n(%)][@]				

Table D. Overview of Adverse Events, Trials MP-4002, MP-4004, and MP-4006

	MP29-02 N=	Placebo N=	Azelastine Hydrochloride N=	Fluticasone Propionate N=
Number of Adverse Events (AE) Reported				
All Treatment-Emergent AEs				
All Treatment-Related AEs				
Number (%) of Subjects with Any AE, n (%)				
All Treatment-Emergent AEs				
All Treatment-Related AEs				
Number (%) Subjects with Serious AEs				
Number (%) Subjects with AEs Leading to Discontinuation				
Number (%) Deaths				
Number (%) Subjects with AEs by Maximum Severity:				
All Treatment-Emergent AEs				
Mild				
Moderate				
Severe				
All Treatment-Related AEs				
Mild				
Moderate				
Severe				

Table E. Adverse Events Leading to Discontinuation of Treatment, Safety Population, Trials MP-4002, MP-4004, and MP-4006

	MP29-02 N=	Placebo N=	Azelastine Hydrochloride N=	Fluticasone Propionate N=
Patients with any AE leading to discontinuation	n (%)	n (%)	n (%)	n (%)
AE leading to discontinuation				
PT	n (%)	n (%)	n (%)	n (%)
PT	n (%)	n (%)	n (%)	n (%)
PT, etc.	n (%)	n (%)	n (%)	n (%)

Table F. TEAEs with an Incidence ≥ 0.5% in MP29-02 Treatment Group, by Decreasing Order of Frequency, Safety Population: Trials MP-4002, MP-4004, MP-4006

Preferred Term	MP29-02 n=	Placebo n=	Azelastine Hydrochloride n=	Fluticasone Propionate n=
Any Adverse Event	n (%)	n (%)	n (%)	n (%)
PT	n (%)	n (%)	n (%)	n (%)
PT	n (%)	n (%)	n (%)	n (%)
PT, etc.	n (%)	n (%)	n (%)	n (%)

Table G. Results of Nasal Examinations, Safety Population: Trials MP-4002, MP-4004, MP-4006

	MP29-02 N (%)	Placebo N (%)	Azelastine Hydrochloride N (%)	Fluticasone Propionate N (%)
Epistaxis, n				
None				
Mild				
Moderate				
Severe				
Nasal Irritation, n				
None				
Grade 1A				
Grade 1B				
Grade 2				
Grade 3				

Grade 4				
Mucosal Edema, n				
None				
Mild				
Moderate				
Severe				
Nasal Discharge, n				
None				
Mild				
Moderate				
Severe				
Mucosal Erythema, n				
None				
Mild				
Moderate				
Severe				
Mucosal Bleeding, n				
None				
Mild				
Moderate				
Severe				
Crusting of Mucosa, n				
None				
Mild				
Moderate				
Severe				

Submit an official response to the NDA by October 18, 2011, or sooner if possible. If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted by: Bowen/10-4-11

Initialed by: Jafari/10-4-11
Pippins/10-3-11
Limb/10-3-11

Finalized by: Bowen/10-4-11

Reference ID: 3024534

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/s/

PHILANTHA M BOWEN
10/04/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: September 23, 2011

To: Brenda Jadney, Associate Director
Regulatory Affairs

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 Re: Clinical Information Request

# of Pages: 3

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Thank you.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Your submission dated April 1, 2011, to NDA 202236 is currently under review and we have the following request for information:

Provide the following tables regarding adverse events leading to discontinuation of treatment. Note that for Table A, the columns entitled "azelastine hydrochloride" and "fluticasone proprionate" refer to the investigational monotherapy comparators evaluated in Trials MP-4002, MP-4002, MP-4004, and MP-4006. Omit monocomparator data for Trial MP-4001. For Table B, the column entitled "fluticasone propionate" refers to the commercially available generic fluticasone product used as the active comparator.

Table A. Adverse Events Leading to Discontinuation of Treatment, Safety Population, Trials MP-4001, MP-4002, MP-4004, and MP-4006

	MP29-02 N=	Placebo N=	Azelastine Hydrochloride N=	Fluticasone Propionate N=
Patients with any AE leading to discontinuation	n (%)	n (%)	n (%)	n (%)
AE leading to discontinuation				
PT	n (%)	n (%)	n (%)	n (%)
PT	n (%)	n (%)	n (%)	n (%)
PT, etc.	n (%)	n (%)	n (%)	n (%)

Note: Monocomparator data (commercial products) omitted for Trial MP-4001

Table B. Adverse Events Leading to Discontinuation of Treatment, Safety Population, Trial MP-4000

	MP29-02 N=	Fluticasone Propionate* N=
Patients with any AE leading to discontinuation	n (%)	n (%)
AE leading to discontinuation		
PT	n (%)	n (%)
PT	n (%)	n (%)
PT, etc.	n (%)	n (%)

*Commercially available generic fluticasone propionate (Boehringer Ingelheim Roxane, Inc.)

Reference ID: 3019897

Submit an official response to the NDA by October 24, 2011, or sooner if possible. If you have any questions, contact Philantha Bowen, Senior Regulatory Project Management Officer, at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted by: Bowen/9-23-11

Initialed by: Jafari/9-23-11
Pippins/9-23-11
Limb/9-23-11

Finalized by: C. Jackson for Bowen/9-23-11

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/s/

COLETTE C JACKSON
09/23/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22203, 22371, and 202236
NDA 11792/S-41
NDA 20114/S-14

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Meda Pharmaceuticals Inc.
265 Davidson Avenue, Suite 300
Somerset, New Jersey 08873-4120

Attention: Brenda Jadney, B.A.
Associate Director, Regulatory Affairs

Dear Ms. Jadney:

Please refer to your New Drug Application (NDA) or Supplemental NDA (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following applications.

NDA 22203 Astepro (azelastine hydrochloride) Nasal Spray
NDA 22371 Astepro (azelastine hydrochloride 0.15% w/v) Nasal Spray
NDA 202236 Dymista (azelastine HCl/fluticasone propionate) Nasal Spray, 137 µg/50 µg
NDA 11792/S-41 Soma (carisoprodol) 250 mg and 350 mg Tablets
NDA 20114/S-14 Astelin (azelastine hydrochloride) Nasal Spray

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Christine Chung, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SANDRA L BARNES
09/15/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: September 13, 2011

To: Brenda Jadney, Associate Director
Regulatory Affairs

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 Re: Clarification of FDA Micro Information Request

# of Pages including cover: 4

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Thank you.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Your submission dated April 1, 2011, to NDA 202236 is currently under review. To facilitate the review process, the FDA provided comments and requested additional microbiology information in a facsimile dated August 31, 2011. In an email correspondence dated September 1, 2011, Meda requested that the FDA further clarify the information request and address the following questions:

Question 1:

Regarding the request for multiple strains of B. cepacia, would three separate ATCC strains of the organism be appropriate? If the manufacturing site does not have an industrial isolate from their purified water system is it required that they still use cells that are acclimated to the environments (eg., warm or cold water).

FDA Response:

For validation of the *B. cepacia* identification test, testing with three separate ATCC strains of the bacterium would be appropriate. If a *B. cepacia* isolate from the manufacturing site is not available, we recommend that you acclimate the ATCC strains to warm or cold water prior to conducting validation studies.

Question 2:
For process controls such as the manufacturing environment, is it acceptable to monitor the production surfaces for Total Aerobic Microbial Count (TAMC) and Total Yeasts and Molds Count (TYMC). Would the TAMC monitoring be adequate to show contamination control? Would the same be acceptable for air monitoring (TAMC and TYMC would be tested in the production areas).

FDA Response:

Monitoring of the air and production surfaces for TAMC and TYMC would be adequate to demonstrate contamination control. Testing for the specific presence of *B. cepacia* will not be necessary.

Question 3:

Is the following approach acceptable? The raw material risk assessment would include those materials (including purified water) which have the potential for microbiological contamination. This would include obtaining water activity data for

Reference ID: 3014347

dry materials, historical data [redacted] **and adding a B. cepacia screen to the purified water.** For raw materials is USP <61> and <62> testing is appropriate or would a separate B. cepacia screen be required

FDA Response:

The approach appears reasonable. The addition of a *B. cepacia* screen for purified water, and the performance of a risk assessment of the raw materials used for formulation, is appropriate and recommended.

If you have any questions, contact Philantha Bowen, Senior Regulatory Project Management Officer, at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meda's original e-mail

Drafted by: Bowen/September 12, 2011

Initialed by: Barnes/September 12, 2011

Finalized by: Bowen/September 13, 2011

Bowen, Philantha

From: Yayac, Cindy [Cindy.Yayac@meda.us]
Sent: Thursday, September 01, 2011 4:01 PM
To: Bowen, Philantha
Cc: Jadney, Brenda
Subject: NDA 202236 - Microbiology Questions

Dear Philantha,

In response to the request from the microbiology reviewer yesterday, and per our discussion today, we have the following questions from one of our facilities that also does micro testing and has had some experience with b. cepacia and may be able to help us expedite this request. We may also receive additional questions from our manufacturing site and will follow-up separately with any they provide.

1. Regarding the request for multiple strains of *B. cepacia*, would 3 separate ATCC strains of the organism be appropriate? If the manufacturing site does not have an industrial isolate from their purified water system is it required that they still use cells that are acclimated to the environments (eg., warm or cold water).

2. For process controls such as the manufacturing environment, is it acceptable to monitor the production surfaces for Total Aerobic Microbial Count (TAMC) and Total Yeasts and Molds Count (TYMC). Would the TAMC monitoring be adequate to show contamination control? Would the same be acceptable for air monitoring (TAMC and TYMC would be tested in the production areas).

3. Is the following approach acceptable? The raw material risk assessment would include those materials (including purified water) which have the potential for microbiological contamination. This would include obtaining water activity data for dry materials, historical data (b) (4) and adding a B. cepacia screen to the purified water. For raw materials is USP <61> and <62> testing is appropriate or would a separate B. cepacia screen be required.

I hope to be able to provide you with an estimate of timing for all of the other outstanding requests by the close of business on Tuesday 9/6.

Cindy Yayac
Senior Manager, Regulatory Affairs

Meda Pharmaceuticals Inc.
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120
Phone: 732-564-2436
Fax: 732-564-2377
(b) (6)
Please note my email address has changed:
cindy.yayac@meda.us

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/s/

PHILANTHA M BOWEN
09/13/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: August 31, 2011

To: Brenda Jadney, Associate Director
Regulatory Affairs

Company: Meda Pharmaceuticals

Fax: 732-564-2377

Phone: 732-564-2362

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 202236 Re: Microbiology Information Request

# of Pages: 3

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Thank you.

NDA 202236
Azelastine-Fluticasone Nasal Spray
Meda Pharmaceuticals

Your submission dated April 1, 2011, to NDA 202236 is currently under review and we have the following microbiology comments and requests for information:

(1) Amend the Microbial Quality section of the drug product Specification (Table 2 of Section 3.2.P.5.1) to include absence of *Burkholderia cepacia* and the method that will be used for *B. cepacia* detection. Your test method should be validated and a discussion of the test methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

(2) Provide the manufacturing controls that will be implemented to limit contamination of the drug product with *B. cepacia*. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for *B. cepacia* in the raw materials is recommended to develop sampling procedures and acceptance criteria.

Submit an official response to the NDA by November 30, 2011, or sooner if possible. If you have any questions, contact Philantha Bowen, Senior Regulatory Project Management Officer, at 301-796-2466.

{See appended electronic signature page}

_____

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted by: Bowen/August 31, 2011

Initialed by: Barnes/August 31, 2011

Finalized by: Bowen/August 31, 2011

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/s/

PHILANTHA M BOWEN
08/31/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202236

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Meda Pharmaceuticals Inc.
265 Davidson Avenue, Suite 300
Somerset, New Jersey 08873-4120

ATTENTION: Richard Fosko, RPh, MPH
Senior Director, Regulatory Affairs

Dear Mr. Fosko:

Please refer to your New Drug Application (NDA) dated April 1, 2011, received April 1, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, 137 mcg and 50 mcg respectively.

We also refer to your April 29, 2011, correspondence, received April 29, 2011, requesting review of your proposed proprietary name, Dymista. We have completed our review of the proposed proprietary name, Dymista and have concluded that it is acceptable.

The proposed proprietary name, Dymista, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 29, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Philantha Bowen at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/25/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202236

FILING COMMUNICATION

Meda Pharmaceuticals, Inc.
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Brenda Jadney, B.A.
Associate Director, Regulatory Affairs

Dear Ms. Jadney:

Please refer to your New Drug Application (NDA) dated April 1, 2011, received April 1, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Dymista (azelastine hydrochloride/fluticasone propionate) Nasal Spray, 137 µg/50 µg (0.1%/0.037%).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is February 1, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 4, 2012.

During our filing review of your application, we identified the following potential review issues:

1. The strength of the findings pertaining to ocular symptoms will be a review issue.

2. From your clinical pharmacology program, it appears that systemic exposure of fluticasone from your combination product is about 44-60% higher compared to reference fluticasone monotherapy product, i.e. generic Flonase. We also noted that you have not conducted an appropriately designed HPA-axis study to evaluate the impact of

this increased exposure of fluticasone on circulating cortisol levels. The clinical impact of the increased fluticasone systemic exposure including the effects on HPA-axis will be a review issue.

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

We have the following comments and/or requests for information:

1. We note that there have been changes to the MP29-02 formulation over the course of development. For labeling purposes, we rely on efficacy and safety data generated from pivotal trials conducted using the to-be-marketed product.

2. Submit revised tables for the following Phase 3, 2-week safety data, omitting Trial MP-4001 from the pooled analysis:

   - Disposition of subjects
   - Overview of adverse events
   - Common adverse events
   - Results of nasal examinations

3. Include iTNSS results in the product label.

4. Carrying forward the last observed score for patients who drop out of the study and then applying repeated measures analysis is problematic. By applying this approach, patients will have the same score over a period of time after they dropout. In addition, patients who drop out for adverse events may have good scores carried forward even though they were not successfully treated. In reviewing the application, we will be applying repeated measures analysis without imputation (i.e. one of your sensitivity analyses) to evaluate the primary and secondary endpoints (TNSS and TOSS) on the ITT population. Submit the analyses results of iTNSS and rTOSS using repeated measures analysis without imputation.

5. In the evaluation of the RQLQ endpoint, it appears that you only included the observed data in the analysis. This approach is not acceptable. The analysis should be conducted on all randomized patients (ITT population). An appropriate strategy to handle missing data should be in place. We will conduct additional analyses during our review of the application.

6. We expect that the drug product used in the pivotal clinical trials to be the same as the to-be-marketed drug product and described in the label. Submit a detailed table summarizing all differences in manufacturing, formulation, and components for development batches of drug product used in the bioequivalence/bioavailability, non

clinical, and clinical studies. Include a thorough discussion of observed *in vitro* differences and evaluate possible impact on the outcome of drug product performance. Present a graphical representation and tabular presentation of performance comparisons for delivered dose, droplet size distribution, particle size distribution, and photographs for plume geometry results for the above mentioned batches.

7. Change the drug product name throughout the labeling (i.e., package insert, carton and container labels) to include the target mass (in mcg) of API delivered per spray (ex-actuator). You may include the percentage concentration in addition, e.g., 137 µg/50 µg (0.1 %/0.037 %). Provide reference to the ex-actuator content data supporting your proposed label spray content and reconcile it with target values listed in specifications.

8. Submit complete CMC information/data for the comparator and placebo drug products used in pivotal clinical studies and compare it with data obtained for the study drugs. Include manufacturing information, specifications, and release and stability data. Submit graphical comparisons of the performance attributes for the monocomparators to the study drugs for each dose.

9. Submit an updated list of manufacturing and testing facilities for the study drugs (including monocomparators) and placebo products used in the pivotal clinical trials and for the to-be-marketed presentations of the drug product. Submit a statement that all facilities are ready for inspection.

10. Combine the release and stability specifications for drug product into a single document. Indicate in this document which attributes are not tested on stability. Specify differences in analytical methods, if any, between release and stability specifications.

11. Provide concise summaries of analytical method validation (MV) data with detailed references to the actual data. Currently, some pages of raw data (e.g., MV reports) are not legible and need to be resubmitted, for example, page 24 of the analytical method validation report for droplet size distribution.

12. Submit a stability data summary as requested during the pre-NDA meeting held on August 17, 2010. Provide graphical presentations and evaluation of observed stability trends for all stability-indicating attributes. Compare drug product performance in different storage conditions/orientations for each presentation of drug product.

13. Include osmolality and viscosity attributes as part of the regulatory drug product specifications, or provide adequate justification for not doing so.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

14. All periods following the numbers that precede the section and subsection headings in the

Table of Contents and throughout the Full Prescribing Information of the package insert must be omitted. For example,

1. INDICATIONS AND USAGE
(b) (4)

We request that you resubmit labeling that addresses these issues by July 5, 2011. The resubmitted labeling will be used for further labeling discussions.

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. The proposed justification for the pediatric waiver does not appear to be adequate at this time. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
06/13/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202236

NDA ACKNOWLEDGMENT

Meda Pharmaceuticals, Inc.
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Richard Fosko, R.Ph., MPH
Director, Regulatory Affairs

Dear Mr. Fosko:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Azelastine/Fluticasone

Date of Application: April 1, 2011

Date of Receipt: April 1, 2011

Our Reference Number: NDA 202236

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 31, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PHILANTHA M BOWEN
04/08/2011
Acting on Behalf of Sandy Barnes

Fosko, Richard

From: Bowen, Philantha [Philantha.Bowen@fda.hhs.gov]
Sent: Monday, December 13, 2010 3:17 PM
To: Fosko, Richard
Subject: RE: IND 77363 - Pre-NDA meeting minutes attached

Thanks Rick,

Meda's minutes have been reviewed by the team. At this time, no addendum will be drafted, since it appears that Meda's minutes simply detail more information. We will, however, retain your submission of the minutes in our records.

Sincerely,

Philantha

From: Fosko, Richard [mailto:Richard.Fosko@meda.us]
Sent: Friday, December 10, 2010 3:48 PM
To: Bowen, Philantha
Subject: RE: IND 77363 - Pre-NDA meeting minutes attached

IND 77,363
Azelastine/Fluticasone Combination Nasal Spray

Hi Philantha,

We reviewed the minutes from our August 17, 2010 meeting and request two items be clarified in the minutes. Attached is a formal copy of our letter to the IND.

Thanks. Have a good weekend.

Rick Fosko
Meda Pharmaceuticals

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Friday, September 10, 2010 9:53 AM
To: Fosko Richard
Subject: IND 77363 - Pre-NDA meeting minutes attached

Hi Rick,

Attached are the meeting minutes for IND 77363 for the meeting held on August 17, 2010. A formal copy will follow in the mail.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service

Reference ID: 3127881

Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3317
Silver Spring, MD 20993
☎301-796-2466
🖷301-796-9718
✉philantha.bowen@fda.hhs.gov

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77363

MEETING MINUTES

Meda Pharmaceuticals, Inc.
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Richard Fosko, R.Ph., MPH
Director, Regulatory Affairs

Dear Mr. Fosko:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Azelastine/Fluticasone.

We also refer to the meeting between representatives of your firm and the FDA on August 17, 2010. The purpose of the meeting was to discuss your drug development program in support of a new drug application (NDA).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Philantha M. Bowen, M.P.H., RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 17, 2010; 2:00 – 3:30 PM EST
Meeting Location:	Building 22, Conference Room 1419
Application Number:	IND 77363
Product Name:	Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray
Indication:	Seasonal Allergic Rhinitis
Sponsor/Applicant Name:	Meda Pharmaceuticals
Meeting Chair:	Badrul A.Chowdhury, M.D., Ph.D., Division Director
Meeting Recorder:	Philantha M. Bowen, MPH, R.N. Sr. Regulatory Management Officer

FDA ATTENDEES

Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary, Allergy, and Rheumatology Products

Philantha Bowen, M.P.H., RN, Sr. Regulatory Management Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Susan Limb, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Jennifer Pippins, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Sally Seymour, M.D., Deputy Director of Safety, Division of Pulmonary, Allergy, and Rheumatology Products

Molly Topper, Ph.D., Pharmacology/Toxicology Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Marcie Wood, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Office of New Drug Quality Assessment

Eugenia Nashed, Ph.D., Chemistry Reviewer, Division of Pre-Marketing Assessment I, Branch II

Craig Bertha, Ph.D., Chemistry Reviewer, Division of Pre-Marketing Assessment I, Branch II

Office of Clinical Pharmacology

Yun Xu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II

Ying Fan, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Office of Translational Sciences

Joan Buenconsejo, Ph.D., Statistical Team Leader, Office of Biometrics, Division of Biometrics II

Feng Zhou, Ph.D., Statistical Reviewer, Office of Biometrics, Division of Biometrics II

SPONSOR ATTENDEES

Sharon Clarke, President, Meda Pharmaceuticals

Harry Sacks, M.D., FAAP, Vice President, Medical & Scientific Affairs, Chief Medical Officer

Alexandar D'Addio, Ph.D., Vice President, Product and Process Development

Richard Fosko, RPh., M.P.H., Senior Director, Regulatory Affairs

Carrie D'Andrea, M.S., Director, Clinical Programs

Carol Sax, Associate Director, Regulatory Affairs

Ulrich Munzel, Ph.D., Head of Biostatics and Information, Meda AB (Meda Germany)

Consultants

(b) (4)

1.0 BACKGROUND

Meda Pharmaceuticals submitted a pre-NDA meeting request dated April 21, 2010, to seek guidance on the development program for azelastine and fluticasone nasal spray and concurrence that the clinical program has addressed the requirements for the combination rule. The Division reviewed the briefing package dated July 19, 2010. In a facsimile dated August 16, 2010, the Division responded the questions contained in Meda's meeting package.

Any discussion that took place at the meeting is captured directly under the original response including any changes in our original position. Meda's questions are in ***bold italics***; FDA's response is in *italics*; and the discussion is in normal font.

2. DISCUSSION

2.1 GENERAL QUESTION: NDA Format

Question 1:

Meda will submit the NDA in eCTD format. Meda requests the Division agreement on format of the SAS datasets along with the format and content of the Modules to be provided in Section 5. Does the Division agree with the proposed format of the SAS datasets along with the format and content of the Modules as described above?

Division Response:

Yes. We agree.

ADDITIONAL COMMENTS

1. *Submit all raw datasets, as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report. In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.*

2. *Include the programs used for creating main efficacy analysis datasets from submitted raw datasets and the programs used for the efficacy and main safety analyses. In addition, provide a document that explains the use of each program.*

3. *Submit the analysis datasets and programs used to generate the specific analyses results contained in the ISE reports.*

Reference ID: 3127881

4. *Submit the analysis datasets and programs used to generate the inferential analyses results in the ISS reports.*

5. *We refer you to the FDA website for additional information and current documents and guidances. Link to Study Data Specifications: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf.*

Discussion:

There was no discussion on question 1 or the additional comments.

2.2 CMC QUESTIONS

Question 2:

If supported by the data, Meda intends to propose degradation product specifications for the finished combination product that are the same as those currently accepted for the individual products. Does the Division agree that this approach is acceptable if supported by the data?

Division Response:

Assuming the data are supportive and there are no new impurities as a result of the formulation of the combination drug product, the approach to propose the same acceptance criteria for azelastine- and fluticasone propionate-related impurities, as are in place for the monotherapy products (approved NDA 22371 and USP monograph for fluticasone propionate nasal spray), is acceptable. Be aware that there may be additional process impurities in the fluticasone propionate drug substance that will need to be controlled at the drug substance level.

Discussion:

Meda requested that the Division provide further clarification and guidance pertaining to the statement, "Be aware that there may be additional process impurities. . . drug substance level." In this request Meda questioned if the Division was aware of specific drug product impurities.

The Division pointed out that USP drug product monographs do not include synthesis related impurities, thus the statement related to process impurities was simply provided as a cautionary comment, nothing more.

Reference ID: 3127881

Question 3:

Meda proposes to submit 30 months of stability data on three registration batches of the product manufactured at the primary site. Additionally, Meda intends to submit stability data on three batches of the finished product manufactured at an alternate site. Minor modifications in a container/closure system may also be addressed. Thus, at a minimum, 3-6 months accelerated and RT stability data will be included in the initial NDA or in a prior approval supplement to support these proposed changes. Does the Division agree with this approach?

Division Response:

Yes, we agree with the approach, as long as you also provide a standard stability commitment (i.e., complete studies, provide results in annual reports, withdraw from market any batches found to be out-of-specification). The acceptability of the alternate site and "minor" container/closure system modifications will depend on the comparability of the stability data from the product produced at that site and with the modifications, to the data from the product from the primary stability site. Comparability will be assessed during review of the NDA.

Discussion:

There was no discussion on question 3.

ADDITIONAL CMC COMMENT

We remind you to include in the development section of your NDA, information and data supporting the comparability of the azelastine HCl and fluticasone propionate monotherapy products to the to-be-marketed combination drug product that were studied in the clinical trials, in terms of formulation, manufacturing, delivery performance (i.e., droplet size distribution, individual drug dose delivery, spray weight, spray pattern), and stability. Refer to the additional comment in our responses and associated discussion for the meeting held on April 29, 2008.

Discussion:

Meda pointed out that the information outlined in the CMC additional comment was submitted to the IND in 2008, based upon an information request received from the Agency in April 2008. The Division responded that the additional comment was intended as a reminder, since the data submitted by Meda was general. Usually, sponsors provide more detailed CMC data in the IND. The Division conveyed to Meda that the information to be submitted should include, but are not limited to, drug formulations and side by side drug comparisons based on current data.

Reference ID: 3127881

2.3 NONCLINICAL QUESTION:

Question 4:

Azelastine hydrochloride (AH) and fluticasone propionate (FP) have been extensively characterized in their respective approved NDAs and published literature. Does the Division agree that presentation of data from the three intranasal toxicity studies for MP29-02 supplemented with existing AH and FP information is sufficient for the Nonclinical Overview and Nonclinical Written/Tabulated Summaries in Module 2?

Division Response:

In general, we agree with your proposal. We remind you to include complete summaries of nonclinical safety information for each of the azelastine hydrochloride and fluticasone propionate monoproducts, in addition to the combination product, in your NDA submission.

Discussion:

There was no discussion on question 4.

ADDITIONAL NONCLINICAL COMMENTS

1. *Refer to ICH Guidance [ICH Q3A(R) and ICH Q3B(R)] for possible qualification requirements of impurities and degradation products. Impurities or degradants of the active ingredients that are identified as structural alerts or genotoxic should be at or below acceptable qualification thresholds to support all clinical studies and for an NDA, as described in the draft FDA Guidance for Industry "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008)".*

2. *Provide safety qualifications for leachables and extractables.*

Discussion:

There was no discussion on the nonclinical additional comments.

2.4 CLINICAL QUESTIONS

Question 5:

Meda's proposed format and content of Safety Summary Tables (i.e. age, gender, race, system organ class) is provided in Section 6.4.6. Does the Division agree with the proposal?

Reference ID: 3127881

Division Response:

Yes, the proposed tabulations are acceptable.

Discussion:

There was no discussion on question 5.

Question 6:

Meda's proposed format and content of Efficacy Summary Tables is provided in section 6.4.6. Does the Division agree with the proposal?

Division Response:

Yes, the proposed tabulations are acceptable.

Discussion:

There was no discussion on question 6.

Question 7:

Meda's perspective is that adequate evidence of safety has been demonstrated in the MP29-02 clinical program. We recognize that an assessment of the adequacy of the data will be a review issue. However, does the Division agree that no further clinical safety studies are required for the proposed SAR indication in patients 12 years of age and older?

Division Response:

No, we cannot agree at this time that no further clinical safety studies will be required.

Discussion:

Meda requested that the Division elaborate on the inability to agree that no further clinical safety studies will be required,. In addition, Meda questioned if any aspect regarding safety had been omitted.

The Division responded that Meda appears to have an adequate clinical program for NDA submission, but the Division could not concur at this time that no additional safety studies will

Reference ID: 3127881

be required, given that issues requiring further safety evaluation may arise at any time, both during the review of the application, as well as after approval.

Question 8:

In previous discussions, the Division commented that a fixed dose combination does not allow for downward titration of the steroid component. MP29-02 dosed at the one spray per nostril twice daily contains the same total daily dosage as the lowest approved fluticasone and azelastine doses (i.e. 200 mcg daily for fluticasone and 548 mcg daily for azelastine). Meda's perspective is that a lower dose MP29-02 study is below the approved doses for each monotherapy and therefore is not required. Does the Division agree that a lower dose MP29-02 is not required for the NDA filing?

Division Response:

A lower dose of MP29-02 is not required for NDA filing. However, we remain concerned about the lack of flexibility of dosage titration with the fixed dose combination. This lack of flexibility will be evaluated in the context of the available safety information, and will be a review issue.

Discussion:

There was no discussion on question 8.

Question 9:

The Division previously requested in the FDA Minutes for April 29, 2008, Meeting that Meda provide in vitro data to demonstrate that MP29-02 has similar product characteristics to the investigational monotherapies used in the clinical program. On August 7, 2008, (Serial No. 0019), Meda submitted data that demonstrated the pharmaceutical comparability of the in vitro dose delivery of the investigational monotherapy products compared to MP29-02. In addition, Meda will provide pharmacokinetic data to show that nasal administration of MP29-02 results in similar systemic levels of each drug compared to the investigational monotherapies used in the clinical program and to the marketed Astelin and Flonase Nasal Sprays. Similar systemic levels of each drug will allow us to appropriately bridge to the preclinical and clinical safety of each of the monotherapies and marketed Astelin and Flonase Nasal Sprays, therefore eliminating the need to conduct special safety trials including a HPA-axis trial. Acknowledging that evaluation of the specific data is a review issue, does the Division agree with this bridging proposal?

Meda also believes this bridging proposal will allow for consideration of MP4001 (which evaluated commercial product monotherapies) as a pivotal trial along with MP4002, MP4004 and MP4006 (which evaluated investigational monotherapies). Does the Division agree?

Reference ID: 3127881

Division Response:

If the systemic exposure from MP29-02 is equal or less than the systemic exposures for fluticasone and azelastine, respectively, from the corresponding commercially marketed monotherapies, then the proposed pharmacokinetic assessments will facilitate bridging to the systemic safety profiles established for the commercial monotherapies. Accordingly, a separate HPA axis effect trial with MP29-02 will not be required if you provide robust pharmacokinetic exposure data. However, the proposed pharmacokinetic data do not account for formulation differences that may alter the efficacy and local safety of locally acting products. Given this limitation, the results from MP4001 will likely be viewed as secondary support for the factorial contribution of azelastine and fluticasone to the efficacy of MP29-02.

Discussion:

There was no discussion on question 9.

ADDITIONAL CLINICAL COMMENTS

1. *The Division finds the proposed indication for the treatment of nasal* (b) (4) *symptoms associated with seasonal allergic rhinitis to be problematic.* (b) (4) (b) (4)

   Discussion:

   There was no discussion on comment 1.

2. *Include in your NDA submission a rationale for the large sample size in MP-4006, which enrolled approximately double the patients enrolled in trials MP-4002 and MP-4004.*

   Discussion:

   There was no discussion on comment 2.

3. *The protocol synopses for trials MP-4002, MP-4004, and MP-4006 do not state whether patients with a history of failed therapy with either Astelin or Flonase were excluded. Based on the information provided, we cannot ascertain whether an appropriate patient population requiring combination therapy was identified for these trials.*

Reference ID: 3127881

Discussion:

Meda began the discussion by reading the Division's comment #3 and pointing out that their program was designed to select patients who were highly symptomatic at baseline. The studies did not specifically exclude patients who have failed therapy with one of the monocomponents. However, Meda commented that the response to treatment is not binary; rather, patients may experience partial relief with either fluticasone or azelastine. The studies demonstrated the efficacy of each monocomponent over placebo and showed the added benefit of the combination. Meda concludes, therefore, that patients who do not respond adequately to the monotherapies receive additional benefit when treated with the combination therapy. Meda also stated that their decision to avoid a failure study design was based on discussion with the Division in 2008. Meda asked if the trials' inclusion and exclusion criteria needed to specify that the patient population would not include patients with a history of failed therapy with either Astelin or Flonase.

The Division agreed that the response to therapy is often not binary and acknowledged that conducting a failure study design is challenging. The Division acknowledged that the communication regarding the selection of an appropriate patient population requiring combination therapy has evolved over time, but remains a consideration. During the last teleconference held between the Division and Meda (April 23, 2009), the Division explained that it is not logical to treat patients who have previously failed to respond to either drug in the combination product, since this would lead to patients receiving unnecessary product. The Division stated that this concern still holds, and the appropriate selection of a patient population will be a review issue. For this reason, the sample sizes of the trials were of particular interest. While criteria excluding patients with failed therapy are not a requirement, the Division recommends that Meda specifically address the concern of appropriate patient selection in the NDA submission.

ADDITIONAL DISCUSSION

Program Design

The Division recommended that Meda address the following issues in the NDA submission: 1) explain the rationale for an additional trial when typically two trials would be sufficient for establishing efficacy, and 2) explain the rationale for the large (doubled) sample size in trial MP-4006.

Meda agreed that they will provide explanation in the application. They added that the rationale for the additional trial and increased sample size was based upon previous trial results. Regarding the decision to conduct trial MP-4006, MP-4001 had yielded striking results, however, the results of MP-4002, while statistically significant, were not of the same magnitude as those for MP-4001, which prompted the company to conduct an additional trial. In addition, the total ocular symptom score (TOSS) had not been prespecified as an endpoint in trial MP-4002, which supported the decision to conduct an additional trial.

The Division reminded Meda that in previous discussions there had been agreement on principles governing the issues of sample size, and asked for explanation of the large size of trial MP-4006. Meda responded that the results of trail MP-4002, which demonstrated a

Reference ID: 3127881

"delta" (effect size) that was smaller than anticipated, prompted the company's decision to increase the sample size in order to be on the safe side. The Division stated that it will be important for Meda to make their case in their application, particularly given that there is no established minimum clinically important difference for seasonal allergic rhinitis. A product associated with a small treatment difference, but a significant p-value driven by a large sample size is undesirable. The Division recommended that Meda reflect back on the minutes of previous meetings during which this issue was discussed.

Meda stated that the treatment difference associated with the combination product as compared to the monocomponents is comparable to that for non-sedating products compared to placebo. The Division responded that cross-study comparisons are fraught with difficulty. Meda replied that they will address the issue of clinical significance to the best of their ability in the NDA submission. Meda also asked whether there were any concerns regarding MP-4002 and MP-4004, to which the Division replied, no.

Clinical Pharmacology

The Division recognized that Meda's PK study is a single-dose (SD) study and questioned what Meda's expectations were for the study. Meda explained that they plan to conduct two PK studies, one for fluticasone and one for azelastine Each PK study will be a single dose PK study with three arms, including the US marketed reference listed product, the proposed combination product, and the mono-product from the pivotal study. Meda expects that a single-dose study will be more sensitive for detecting possible drug interactions compared to a multiple dose study. In addressing the Division's questions pertaining to whether Meda considered a multiple-dose (MD) study and why Meda believes a single-dose study is sufficient, Meda explained that the decision to conduct a SD study outweighs the disadvantages. Single-dose studies are preferred because of their sensitivity to Cmax. The Division asked Meda if they were confident that MD studies would not provide additional information, if only small differences were observed in SD studies. Meda replied that unlike SD studies, MD studies are not sensitive to Cmax. The Division pointed out that if MD comparisons are performed, they may provide additional information. If differences are seen in SD studies, they may in turn be magnified in MD studies. The Division conveyed that if an interaction is present, it may be seen in the MD and not in the SD study. Therefore, the Division recommended that Meda provide a justification in the NDA submission explaining why the SD study is sufficient to address drug-drug interaction. Additionally, the Division pointed out that the proposed product may be used chronically, so MD data may be of greater clinical relevance. Meda stated that they are not seeking a chronic indication, such as PAR or VMR for the product. The Division commented that the label would not limit use.

Fluticasone Monotherapy

The Division questioned Meda about their intentions regarding labeling and the anticipated patient population in the market setting. Meda replied that no definite determination has been made (b) (4)

(b) (4)

Reference ID: 3127881

(b) (4)

[redacted]

CMC

As a part of the NDA submission, the Division recommended that Meda submit: 1) phase III information on the *in vitro* characteristics of the combination and monotherapy products so that comparisons can be drawn; 2) tables outlining the changes that have occurred during development; and 3) complete CMC information for both the combination product and the final monoproducts (as if they were being submitted for approval) along with side-by-side comparisons of the comparators with the combination.

The Division noted that the combination product and fluticasone monotherapy are suspensions, whereas the azelastine monotherapy and placebo are both dispersions of microcrystalline cellulose excipients (with or without solubilized azelastine), which do not lend themselves to simple comparisons. Meda conveyed their intent to show the characteristics of fluticasone in suspension and on stability. The Division recommended that Meda submit all related data and tables. The Division reminded Meda that the demonstrated differences should be driven by clinical, and not *in vitro,* characteristics.

The Division reiterated that combination products, in principle, are for convenience. Meda replied that the azelastine was initially large in volume. So, in addition to convenience, Meda believes that the reduced volume will allow for better retention.

Meda's Summary

Meda provided the following as a summary of the Division's position on the questions and comments discussed during the meeting: 1) the CMC response to question 2 and the additional comment were intended to be advisory; 2) the clinical response to question 7 conveys that safe and adequate information needs to be provided in the NDA and the Division may request additional safety information; and 3) the additional clinical comment 3 and the subsequent discussion clarified that Meda will need to provide justification for the selected patient population, the number of trials conducted, and the chosen sample size; provide a rationale for the decision to conduct single-dose PK studies; and present CMC data using graphs, tables, etc., for both the combination product and monoproducts, including side-by-side comparisons.

With regards to the NDA submission, Meda plans to submit the application near the end of the first quarter in 2011.

Reference ID: 3127881

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There were no outstanding action items for this meeting.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Reference ID: 3127881

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77363	GI-1	MEDA PHARMACEUTICALS MEDA PHARMACEUTICALS INC	AZELASTINE/FLUTICASONE COMBINATION NASAL

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
09/10/2010

FOOD AND DRUG ADMINISTRATION

Meeting Type:	Regulatory Briefing
Meeting Category:	Guidance
Meeting Date and Time:	April 17, 2009 1:00-3:00 PM
Meeting Location:	Food and Drug Administration 10903 New Hampshire Ave. White Oak Central Shared Use, Room 2047 Silver Spring, MD 20993
Meeting Subject:	Interpretation of the Combination Rule for Allergic Rhinitis Products
Meeting Requestor:	Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary and Allergy Products
Meeting Chair:	John K. Jenkins, MD, Director Office of New Drugs
Meeting Recorder:	Philantha Montgomery Bowen, MPH, RN, Senior Regulatory Management Officer. Division of Pulmonary and Allergy Products

Meeting Attendees:

Janet Woodcock, MD, Director, CDER

John Jenkins, MD, FCCP, Director, OND

Robert Temple, MD, Director, OMP and ODEI

Curtis Rosebraugh, MD, Deputy Director, ODEII

Badrul A. Chowdhury, MD, PhD, Director, DPAP

Lydia Gilbert-McClain, MD, Deputy Director, DPAP

Lee Ripper, ADRA, ODEII

Sally Seymour, MD, Deputy Director for Safety, DPAP

Susan Limb, MD, Clinical Reviewer, DPAP

Philantha Bowen, MPH, RN, Senior Regulatory Management Officer, DPAP

1.0 BACKGROUND

MEDA Pharmaceuticals opened an IND on April 2, 2007 for a development program for a fixed dose combination nasal spray product of azelastine hydrochloride and fluticasone propionate for allergic rhinitis. Both azelastine and fluticasone are approved as individual monotherapies for allergic rhinitis symptoms. In addition to MEDA, other companies have submitted fixed dose combination development programs for allergic rhinitis to the division that have challenged the division's interpretation of the Combination Rule for allergic rhinitis drugs.

The "Combination Rule" for fixed combination prescription drugs codified in 21 CFR 300.50 states:

"Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

The regulation for monograph drugs [21 CFR 330.10(a) (4) (iv)] states:
"An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effects(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population."

The current DPAP position is that when two or more drugs are combined into one dosage form, this combination should be a scientifically rational combination. The Division has accepted products containing antihistamines and nasal decongestants as rational combination products and this is consistent with the permitted combinations of the cough, cold, allergy, bronchodilator, and antihistamine drugs OTC monograph (21 CFR 341.40). Based on this reasoning, the currently approved prescription combination products for allergic rhinitis have been anti-histamine/decongestants and the labeled indication for these products specifically includes nasal congestion. For example the labeled indication for Allegra D (fexofenadine hydrochloride and pseudoephedrine hydrochloride) 24 Hour Extended release tablets states:

Reference ID: 3127881

"Indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include . . . nasal congestion."). The labeling or this product also states that *"ALLEGRA- D 24 HOUR should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired."*

Drug classes for allergic rhinitis include antihistamines, inhaled corticosteroids, and the leukotriene receptor antagonist, montelukast (see table below). In addition, oral antihistamines have been combined with nasal decongestants for additional decongestant relief.

Table of Product classes approved for allergic rhinitis symptoms

Drug class	Formulation	Example/Indication
Corticosteroid	Nasal spray	*Fluticasone propionate (Flonase®)
Antihistamine (oral formulation)	Oral tablets, solution	Levocetirizine (Xyzal)
Antihistamine (nasal spray)	Nasal spray	Azelastine (Astelin®); Astepro®
Leukotriene antagonist (oral)	Oral tables, granules, chewable tablets	Montelukast (Singulair)
Anti-histamine/decongestant fixed dose combination	Oral tablets/solutions	Clarinex-D, Allegra-D

The current rhinitis practice parameters describe the different drug classes that are used to treat allergic rhinitis but do not make recommendations for specific add-on or step-wise therapy. The most recent rhinitis joint practice parameters from the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) state that in cases where monotherapy is insufficient, substitution or addition of another class of drug could be considered but caution that combination therapy for rhinitis may not provide a major therapeutic advantage to balance the cost of this approach (*J Allergy Clin Immunol*. 2008 August; 122 (2 Suppl 1): S1-S84).

In regards to the specific combination of an intranasal antihistamine with an intranasal corticosteroid, the rhinitis practice parameters, note that there is limited data, but that this combination may be considered for some patients, particularly those with mixed rhinitis. While the parameters do not specifically define "mixed rhinitis," this is a commonly used term that includes both allergic and non-allergic forms of rhinitis. The practice parameters also note that there is inadequate data on the optimal interval between administrations of the two nasal sprays. Without an adequate interval between sprays, it is possible that one nasal spray may wash the other spray medication out and limit efficacy.

Reference ID: 3127881

A recent publication in NEJM also notes that data are lacking from rigorous studies to demonstrate that combination therapy with antihistamines and nasal corticosteroids is superior to nasal corticosteroids alone (*N Engl J Med.* 2005; 353:1934-44). In addition, the Allergic Rhinitis Impact on Asthma (ARIA) document (endorsed in the EU and developed through a WHO workshop) states that insufficient data are available to make a recommendation concerning the combined use of H_1 -antihistamines and intranasal corticosteroids (*Allergy.* Supplement 86; Volume 63: 2008).

The Division seeks feedback on their interpretation of the combination rule (21 CFR 300.50) for fixed-dose combination products for allergic rhinitis. In general the division's interpretation of the combination rule for allergic rhinitis has been based on the following principles:

1) The combination of an anti-histamine and a nasal decongestant is a rational combination (consistent with 21 CFR 341.40(b)) and such combination products can be approved using a pharmacokinetic program.

2) When a pharmacokinetic program for an antihistamine and a decongestant fails to show bioequivalence, or when a novel combination product is proposed (e.g. combination of an antihistamine and leukotriene antagonist) approval of such combination products is based on clinical studies.

3) Clinical studies to support approval of allergic rhinitis fixed dose combination products use a factorial design with the intent of showing that the combination product is statistically superior to each component on relevant clinical endpoints, such as showing an antihistamine and decongestant combination product is superior to the antihistamine component alone for relief of nasal congestion.

31 Pages have been Withheld in Full as b5 (Intra-Agency Memoranda/Deliberative Process) immediately following this page.

Reference ID: 3127881

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type A
Meeting Category:	Special Protocol Assessment
Meeting Date and Time:	April 29, 2008 9:00-10:00 AM
Meeting Location:	Building 22, Conference Room 1415
Application Number:	IND 77,363
Product Name:	Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray
Received Briefing Package	April 15, 2008
Sponsor Name:	MEDA Pharmaceuticals
Meeting Requestor:	Richard Fosko, R.Ph., MPH Director, Regulatory Affairs
Meeting Chair:	Badrul A.Chowdhury, M.D., Ph.D., Director Division of Pulmonary and Allergy Products
Meeting Recorder:	Philantha M. Bowen, MPH, R.N. Sr. Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary and Allergy Products

Philantha Bowen, M.P.H., RN, Sr. Regulatory Management Officer, Division of Pulmonary and Allergy Products

Sally Seymour, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products

C. Joe Sun, Ph.D., Pharmacology/Toxicology Team Leader, Division of Pulmonary and Allergy Products

Jean Wu, M.D., Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products

Reference ID: 3127881

Office of New Drug Quality Assessment

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I, Branch II

Eugenia Nashed, Ph.D., Quality Reviewer, Division of Pre-Marketing Assessment I, Branch II

Office of Clinical Pharmacology

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2

Sponsor Attendees

Richard Spivey, PharmD, Ph.D., Senior Vice President, Research and Development

Harry Sacks, M.D., Vice President, Medical and Scientific Affairs

Cary Sax, Associate Director, Regulatory Affairs

(b) (4)

Reference ID: 3127881

1.0 BACKGROUND

MEDA Pharmaceuticals submitted a Special Protocol Assessment (SPA) dated December 21, 2007, for the clinical protocol MP4002 for the azelastine/fluticasone combination nasal spray. On January 31, 2008, the Division responded to MEDA's SPA request.

MEDA Pharmaceuticals submitted a Type A meeting request, dated February 29, 2008, to discuss the Agency's comments and responses regarding the SPA. The briefing package, dated April 14, 2008, was reviewed by the Division. On April 28, 2008, the Division responded to MEDA's questions via facsimile. The content of the fax is printed below.

Any discussion that took place at the meeting is captured in section 3.0 including any changes in our original position. MEDA's questions are in ***bold italics*** and FDA's response is in *italics*; the discussion is in normal font.

2.0 QUESTIONS

2.1 QUESTION 1

Question 1:

Does the Division agree that patients with moderate/severe nasal symptoms of seasonal allergic rhinitis, as defined by ARIA, is an appropriate target population for this drug?

Division Response:

We do not agree. We have expressed concerns that you have not provided evidence that a population for this combination product exists. The ARIA Guidelines presented do not alleviate these concerns. The ARIA classification for allergic rhinitis classifies allergic rhinitis based upon intermittent and persistent symptoms and is not universally adopted in the United States. In particular, this type of classification is not used for approval of therapeutics for allergic rhinitis.

The combining of different products to control symptoms of SAR is the practice of medicine. Single ingredient products containing azelastine or fluticasone propionate are approved for treatment of symptoms of seasonal allergic rhinitis. The combination product that you are proposing to develop is targeted to treat the same symptoms that the single ingredient products are already indicated for. Demonstrating significantly greater symptom relief with the combination product over its individual single active ingredients will not be sufficient to demonstrate that both azelastine and fluticasone propionate contribute to the effectiveness of the combination. Demonstration of greater symptom relief with the combination product over its active ingredients (for the exact same symptoms) is likely to be due to the fact some patients may not be responding to

Reference ID: 3127881

azelastine while responding to fluticasone propionate, and vice versa. Rationale based on pharmacodynamic reasoning, such as mechanism of action, onset of symptom relief, etc., are also not sufficient to justify this combination product.

As stated before, combining products eliminates flexibility with dosage titration and potentially exposes patients to unnecessary medication; and thus unnecessary risk.

2.2 QUESTION 2

Question 2:

Does the Division agree that our proposed inclusion/exclusion criteria will study a population of patients with moderate/severe rhinitis?

Division Response:

We do not agree. We do not have specific criteria using the TNSS to define what constitutes moderate or severe allergic rhinitis.

2.3 QUESTION 3

Question 3:

Does the Division agree that the proposed dosage of the individual components of the fixed dosage product (that are within the labeling for those marketed products) is appropriate for study in the MP4002 study?

Division Response:

We remain concerned about the lack of flexibility of dosage titration with the fixed dose combination (FDC). We acknowledge your explanation and ask you to make the reasoning in the NDA, if you are to develop this product. This will be a review issue.

2.4 QUESTION 4

Question 4:

Does the Division agree that no new corticosteroid-specific safety issues are anticipated with the fixed dose combination product that would require MEDA to study a dosage that is lower than the recommended dosage in the fluticasone label? This question is predicated on the assumption that adequate pK studies do not show

Reference ID: 3127881

an appreciable enhancement of absorption of fluticasone. In addition, it assumes that appropriate long term studies support the safety of the combination product.

Division Response:
We cannot agree. Your question is based upon assumptions that are unknown at this time. Your FDC, as well as, the individual monotherapies, with new formulations represent new products. The safety and efficacy of each of these products have not been established. Therefore, we cannot agree that no new corticosteroid safety issues are anticipated.

2.5 QUESTION 5

Question 5:

If the Division still does not agree that we have appropriately applied the specific elements of the combination rule stated above, then we respectively request the opinion of the Director of the Office of Drug Evaluation II on the above issues. In addition, we would also request input from the Office of Medical Policy on the Division's interpretation of these elements of the combination rule under these circumstances.

We believe we have addressed your questions adequately and the responses can be discussed at the face-to-face meeting.

ADDITIONAL COMMENT: CMC

We note that four new suspension nasal spray drug products were manufactured for the use in this IND, i.e., azelastine hydrochloride/fluticasone propionate combination nasal spray (different formulation from the original IND submission), two single-active-comparator nasal sprays, and a placebo nasal spray. Any further development in the clinical program must be accompanied by the submission of the formal in vitro *characterization studies for these drug products, as described in our Guidance "Nasal Spray and Inhalation Solution, Suspension, and Drug Products". In particular, provide the dose performance data (e.g., emitted dose, spray content uniformity, droplet size distribution, etc.) that characterizes the combination nasal spray product and the two monotherapy products (azelastine hydrochloride nasal spray and fluticasone propionate nasal spray). Provide these data in a side-by-side presentation using graphs, in order to demonstrate the pharmaceutical comparability of the* in vitro *dose delivery for the single component drugs relative to the combination product.*

3.0 DISCUSSION

Reference ID: 3127881

MEDA began the discussion seeking clarification on an appropriate patient population and a better understanding of application of the combination product rule. MEDA outlined the following points for clarification:

- An understanding of the Division's position of why it is a problem that the proposed combination product is targeted to treat the same symptoms as the single product ingredients;
- An explanation as to why the combination product, if shown to demonstrate greater symptom relief over the single ingredients, is not sufficient;
- Discussion and clarity of the Division's position that greater symptom relief with the combination product over the active ingredients may be a result of some patients responding to one single ingredient over the other.

MEDA informed the Division that the rationale for the combination product was based upon input from allergists who noted they treat many of their SAR patients with both azelastine and fluticasone nasal sprays. MEDA acknowledged the Division's comment that combining different products to control symptoms of SAR is the practice of medicine. However, MEDA explained that the combination product would be better than the individual ingredients because patients would not have to take four sprays of medication at a time. With the individual components, compliance becomes an issue; thus leading to treatment failures and unmet patient needs. MEDA suggested that the patient population would be those who have failed common treatments regimens and those who would be inconvenienced by taking two single drug products. In terms of safety, MEDA commented that combining the two products versus the individual components would not alter the safety. In fact, the product will be effective and pose less of a risk. MEDA cited examples of other combination products that also treated the same disease, e.g. LABA and ICS for asthma. MEDA asked the Division to provide its expectation of efficacy for the combination product.

The Division responded that the combining of two drugs to treat the same symptoms of a disease is problematic. The Division noted that the combination of azelastine and fluticasone nasal spray is approved as Duonase in India. The Division or MEDA's consultants did not know the specific background of the premise of Duonase approval in India. The Division mentioned that at a recent meeting (b) (4) where one of the MEDA consultants (b) (4) spoke at an academic session, a comment was made from the audience that suggested that the premise of this combination product is that it treats two different types of rhinitis: allergic and non-allergic. The Division commented that such a premise would seem reasonable. The Division noted that MEDA proposes the combination product for the same indication, symptoms of SAR. While the proposed combination may be a choice in the practice of medicine, it is not necessarily rationale as a fixed dose combination. If we look at the cough, cold, allergy, bronchodilator, and antihistamine drugs OTC monograph (21 CFR 341), permitted combinations are described. The combinations described include components that treat a different aspect of the disease, e.g. antihistamine and decongestant or antihistamine and antitussive. The

Reference ID: 3127881

monograph does not allow combination of two drugs that treat the same aspect of the disease, e.g. antihistamine and antihistamine.

The next issue is the combination rule, i.e. that each component makes a contribution to the claimed effects. With the proposed program, MEDA would use the same endpoint, total nasal symptom score (TNSS), to evaluate the efficacy of the combination product and each component. This is problematic because some patients may not respond to one component, but yet respond to the combination; and use of the same endpoint will not discriminate. For example, if a patient has failed azelastine therapy, but responds to the combination product, then it could imply that the response is toward the effects of the steroid; however the patient would receive the combination product where one component provides no benefit, but yet exposes them to unnecessary risk. In addition, the Division raised the possible safety concern regarding the lack of flexibility for dosage titration for the proposed combination product.

MEDA responded that patient response to the combination can be viewed as a synergistic effect. In terms of treatment failure, MEDA stated that "treatment failure" could mean that patients failed to get complete symptom relief. Moreover, MEDA pointed out that for any combination product it may be difficult to determine which component is providing the benefit; hence, randomized studies are used. MEDA questioned the Division as to why this approach could not be utilized with the proposed product. The Division addressed the combination product referenced, LABA and ICS, which have different endpoints to measure disease benefit. In MEDA's proposed program, however, the endpoints are the same and the product is aimed at treating the same aspects of the disease with the two drugs. With such a design, the Division reiterated that it is difficult to determine the contribution of each component.

MEDA noted that there are approved combination products that have the same endpoints (e.g. analgesics); and questioned the application of the combination rule in this situation. The Division could not comment on the application of the combination rule for those particular situations. MEDA was informed of the recent regulatory action taken on a combination product that addressed benefit on the same aspects of disease. The Division stated that it would be MEDA's choice on whether to pursue the study using the same endpoints to measure disease benefit, but MEDA should understand the Division's concerns.

MEDA asked whether other endpoints, such as onset of action, may address the Division's concerns. The Division did not think that onset of action will demonstrate the expected outcome. The Division responded that different methods are risky, however, innovation is encouraged.

The Division, acknowledged MEDA's request to have clarification of the combination rule, and informed MEDA of three aspects to be considered for combination products:

- CFR 341.50 outlines the lists of monographs for combination products that are permitted by law. In addition, the appropriate language for the label is provided, as well as, separate indications for each of the drug components. As discussed

Reference ID: 3127881

earlier, this approach does not provide for combining products that treat the same aspect of the disease. The rationale outlined in CFR 341.50 is sensible, and there is no reason that the same rationale would not apply for prescription products.

- Per CFR 300.50 each component has to make a contribution to the claimed effect. As discussed earlier, the Division stated that it will be difficult to determine the contribution of each component for MEDA's combination product.

- Per CFR 300.50, special cases are allowed if a component is added to enhance the safety or effectiveness of the principle active component. MEDA's combination product does not fit this special case.

MEDA commented that for some combination products, i.e. analgesics, have the same endpoints and the individuals components of the product, as well as the combination, have been superior to placebo. MEDA does not understand how the combination rule precludes development of their combination product. MEDA verbalized their disagreement with Division's position and commented that the pathway for their proposed product for allergic rhinitis is halted.

The Division informed MEDA that consultation and collaboration had been sought with other offices in the Agency, therefore the position taken had not been in isolation. The pathway forward may be for MEDA to formally dispute the Division. The dispute process may be a way to seek the direct involvement of the Office Director. At this point, it will be MEDA's choice to pursue the clinical development program. The Division commented that there appears to be no safety risk in MEDA conducting the study.

The Division recommended to MEDA that if product development is pursued, the CMC information (performance in terms of emitted dose and droplet size distribution) must be evaluated and addressed carefully and referred MEDA to the CMC additional comment provided in the Division's responses. In addition, since each monotherapy represents a new product, one API is in solution (azelastine nasal spray) and the other API is a suspension (fluticasone nasal spray), it was recommended that MEDA address these differences in a side-by-side comparison format.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Reference ID: 3127881

Drafted by: Bowen/May 2, 2008

Initialed by: Qiu/May 13, 2008
Seymour/May 9, 2008
Al Hakim/May 8, 2008
Peri/May 8, 2008
Nashed/May 8, 2008
Sun/May 8, 2008
Wu/May 8, 2008
Chowdhury/May 16, 2008

Finalized by: Bowen/May 19, 2008

Reference ID: 3127881

Linked Applications	Sponsor Name	Drug Name
IND 77363	MEDA PHARMACEUTICALS MEDA PHARMACEUTICALS INC	AZELASTINE/FLUTICASONE COMBINATION NASAL

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/s/

PHILANTHA M BOWEN
05/19/2008

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type A
Meeting Category:	Other
Meeting Date and Time:	September 10, 2007 1:00-2:00 PM
Meeting Location:	Building 22, Conference Room 1417
Application Number:	IND 77,363
Product Name:	MP29-01 (azelastine hydrochloride and fluticasone propionate) Nasal Spray
Received Briefing Package	August 1, 2007
Sponsor Name:	MedPointe Pharmaceuticals
Meeting Requestor:	Michael I. Bernhard, Ph.D. Senior Director, Regulatory Affairs
Meeting Chair:	Badrul A.Chowdhury, M.D., Ph.D., Director Division of Pulmonary and Allergy Products
Meeting Recorder:	Philantha M. Bowen, MPH, R.N. Sr. Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary and Allergy Products

Colette Jackson, Regulatory Project Manager, Division of Pulmonary and Allergy Products

Philantha Bowen, M.P.H., RN, Sr. Regulatory Management Officer, Division of Pulmonary and Allergy Products

Sally Seymour, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products

Susan Limb, M.D., Clinical Reviewer, Division of Pulmonary and Allergy Products

Reference ID: 3127881

C. Joe Sun, Ph.D., Pharmacology/Toxicology Team Leader, Division of Pulmonary and Allergy Products

Jean Wu, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products

Office of New Drug Quality Assessment

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I, Branch II

Eugenia Nashed, Ph.D., Division of Pre-Marketing Assessment I, Branch II

Office of Clinical Pharmacology

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2

Sponsor Attendees

Richard Spivey, PharmD, Ph.D., Senior Vice President, Research and Development

Harry Sacks, M.D., Vice President, Scientific and Medical Affairs

Alexander D'Addio, Ph.D., Vice President, Product and Process Development

Michael Bernhard, Ph.D., Senior Director, Regulatory Affairs

Richard Fosko, R.Ph., MPH, Director, Regulatory Affairs

Debra Iorio, Associate Director, Regulatory Affairs (CMC)

John Higsoh, MBA, B.S., Director of Project Management

Reference ID: 3127881

1.0 BACKGROUND

In a facsimile, dated May 21, 2007, the Division provided comments to MedPointe's initial IND submission dated April 2, 2007. The FDA informed the sponsor that their clinical program will need to establish the contribution of each drug component to the overall safety and efficacy of the combination drug product. In addition, the FDA commented that the proposed comparator monotherapies will have pharmaceutic differences from the proposed combination product; therefore, selection of appropriate comparators was highly recommended.

On June 25, 2007, the Division met with MedPointe via teleconference to clarify the comments of the May 21, 2007, facsimile. The FDA maintained its position regarding the selection of appropriate comparator monotherapies for the proposed combination product. The FDA recommended that MedPointe submit their proposal with rationale and any data to support their position and request a meeting for further discussion.

MedPointe Pharmaceuticals submitted a Type A meeting request, dated July 31, 2007, to seek guidance on the clinical program for Azelastine/Fluticasone combination product for the treatment of nasal symptoms of allergic rhinitis in adults and children 12 years of age and over. The briefing package, dated July 31, 2007, was reviewed by the Division. On September 7, 2007, the Division responded to MedPointe's questions via facsimile. The content of the fax is printed below.

Any discussion that took place at the meeting is captured in section 3.0 including any changes in our original position. MedPointe's questions are in ***bold italics*** and FDA's response is in *italics*; the discussion is in normal font.

2.0 QUESTIONS AND COMMENTS

Introductory comment

According to 21CFR300.50, two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects. Your development program should demonstrate the efficacy and safety of the fixed-combination drug and the contribution of each component to the combination. Determination of the appropriate comparator monotherapy treatment arms for the pivotal studies is critical to your development program. One option would be to develop monotherapies that are essentially the combination product minus one of the active ingredients. This may minimize the pharmaceutical differences between the combination product and the monotherapy components. However, as you note, one potential problem is that removal of an active drug substance from your combination product may change the properties of the monotherapy. This complicates your development program and may be difficult to address.

Reference ID: 3127881

You propose the following monotherapy comparators, Flonase Nasal Spray and Astelin nasal spray. As stated previously, there are pharmaceutical differences between your combination product and your proposed monotherapy comparators which may significantly impact efficacy and safety, complicating interpretation of clinical trial results. If you wish to pursue using these marketed products as the monotherapies in the pivotal studies, you would need to adequately demonstrate the comparability of fluticasone delivered as Flonase and fluticasone delivered via your combination product, as well as, the comparability of azelastine delivered as Astelin and azelastine delivered via your combination product. Demonstration of comparability is quite a high hurdle and would include in vitro, pharmacokinetic, and pharmacodynamic data. Because of the pharmaceutical differences and lack of an objective pharmacodynamic endpoint for allergic rhinitis, demonstration of comparability is likely not feasible. Furthermore, blinding of such commercial comparators in pivotal studies would be problematic due to differences in the delivery systems. Incorporating appropriate dummy products for blinding would introduce additional issues regarding spray volumes. Thus, we do not see a path forward for using Flonase and Astelin as the comparator monotherapies.

In addition, according to 21CFR300.50, the combination should be safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Therefore, you need to identify a patient population that requires such a combination product. Your clinical development program should evaluate the proposed combination product in the proposed patient population that requires concurrent therapy with both azelastine and fluticasone propionate. Identification of such a patient population may be a challenge for your development program.

2.1 QUESTION 1

Question 1:

We plan to demonstrate the clinical efficacy and safety of our proposed combination drug product through two pivotal comparative, placebo-controlled clinical trials and to demonstrate clinical safety in an additional 12-month trial, as proposed in our IND. The proposed safety study should provide adequate data to determine the safety of the proposed formulation, delivery device, and dosing schedule. Considered along with the proposed toxicology program (IND 77-363 initial submission), does the Division agree that safety issues are adequately addressed.

FDA Response to Question 1:

The proposed safety program (two pivotal placebo-controlled trials and a 12 month clinical safety trial) appears reasonable, assuming selection of appropriate monotherapy comparators in the pivotal studies as discussed in the introductory comment. However, additional safety data may be required depending on the adverse event profile and systemic exposure observed for the proposed combination drug product.

Reference ID: 3127881

2.2 QUESTION 2

Question 2:

Does the Division agree that Flonase is an appropriate control for the proposed 12-month clinical safety trial?

FDA response to Question 2:

No, we do not agree. While inclusion of an active comparator such as Flonase or Astelin is your choice, the proposed 12-month safety trial should include a placebo treatment group.

2.3 QUESTION 3

Question 3:

We are proposing a drug/drug combination product that, (b) (4) ***, may have significant clinical advantages over the commercially available monotherapies.*** (b) (4) ***Combining a soluble and an insoluble API in a single nasal spray formulation presents unique issues, rendering this an atypical situation that requires careful consideration. Does the Division agree that this proposed combination product is atypical and as such may require an alternative approach that will also satisfy the combination product rule?***

FDA Response to Question 3:

We agree that your combination product poses some unique issues that may be difficult to address. However, this does not change our interpretation of what is necessary to satisfy the combination product rule.

We note that you propose your combination product will have significant advantages over commercially available monotherapies. If you intend to pursue a superiority claim, we recommend you discuss the feasibility of such a claim with the Agency.

Also, we note a potential disadvantage of the proposed combination over the commercially available monotherapies. For example, a fixed-dose combination does not allow the downward dose titration or as needed administration of fluticasone propionate, which are options with the commercially available monotherapy.

2.4 QUESTION 4

Question 4:

Formulating monotherapy comparators with identical formulations to the proposed combination product but without one or the other of the APIs may result in changes to

Reference ID: 3127881

the formulation that render the monotherapies unsuitable for the proposed use. For example, removing fluticasone may change the viscosity and/or spray pattern, droplet size, or plume geometry of the Division proposed azelastine monotherapy comparator when compared to the combination formulation. Similarly, removing azelastine may cause changes. Thus, the monotherapies proposed by the Division may demonstrate differences between these monotherapies and the proposed combination product and thus not be consistent with the Division's intent when proposing these monotherapies. Does the Division agree?

FDA Response to question 4:

As stated in the introductory comment, we acknowledge the potential for your monotherapy product to be affected by removal of one of the APIs. This could complicate your development program and may be difficult to address.

2.5 QUESTION 5

Question 5:

The proposed combination product cannot use the same nasal spray device as each approved monotherapy because Astelin and Flonase use different metered spray pumps. Using the proposed combination product spray pump with the Division's recommended, specially formulated monotherapy comparators may affect the efficacy of the monotherapy comparators as compared to the approved monotherapies. Using the approved monotherapies assures the comparators will have the efficacy and safety physicians associate with these products.

a. ***Does the Division agree that the use of specially formulated monotherapy comparators with a spray pump designed for use with the proposed combination product may alter the known efficacy of the monotherapies?***

b. ***Does the Division agree that using the monotherapies proposed by the Division with the proposed combination product spray pump may not meet the Division's intent in proposing the use of these specially formulated monotherapies?***

FDA Response to question 5:

Refer to the introductory comment and response to Question 4.

2.6 QUESTION 6

Question 6:

Reference ID: 3127881

The use of specially formulated monotherapies for comparator controls in pivotal clinical trials provides comparator data that are only directly applicable to the specially formulated monotherapy comparators and may not reflect either the efficacy or safety of the approved monotherapies. Data derived from the use of these specially formulated monotherapies will not provide prescribing physicians usable information about the approved commercial monotherapies compared to the proposed combination product to assist in their prescribing decisions. We believe the use of the approved monotherapies will provide physicians the information they need to assess the value of the proposed combination.

c. ***Does the Division agree?***

d. ***If not, can the Division expand upon their position and how the results of the studies using the specially formulated comparators would be explained in the package insert and provide usable information for the physician?***

FDA Response to question 6:

c) We do not agree. Refer to the introductory comment. The fixed-combination drug regulations do not stipulate that clinical trials establish a comparison with commercially available monotherapies. d) For an example of a description of clinical studies to support approval of a combination product, we refer you to the Symbicort Inhalation Aerosol product label.

3.0 DISCUSSION

MedPointe began the discussion by acknowledging the FDA's position and indicated they planned to make the individual monotherapies (fluticasone and azelastine) in the same vehicle and same device as the combination product for use in clinical studies. MedPointe then outlined the following points for clarification:

- Comparability of the proposed combination product to Flonase or Astelin®
- Conducting the proposed 12-month study and inclusion of a placebo
- Foreseen blinding difficulties
- Superiority claim for the combination product was no longer being considered
- Identification of an appropriate patient population

MedPointe questioned the FDA as to whether the need existed to show comparability of the combination product to the approved products, Flonase or Astelin®, prior to approval. The Division responded that since the comparator monotherapies are now the

Reference ID: 3127881

fluticasone and azelastine products in the same vehicle and device as the combination product, then comparability data with the approved products, Flonase and Astelin was not necessary. However, the FDA asked MedPointe if they could actually manufacture these monotherapies since they indicated potential difficulties in the meeting package. MedPointe responded that they are optimistic that the products could be made; however, they have not manufactured the monotherapies yet. MedPointe indicated that fluticasone would be a suspension and azelastine would be a solution that was processed to demonstrate the characteristics of the proposed combination product.

The FDA questioned MedPointe regarding whether the final placebo formulation would be solution or suspension. MedPointe stated that the final formulation would not be a true suspension but they could not provide any more details at this point. The FDA stated that an *in vitro* performance comparison of the fixed dose combination product to the individual single ingredient formulations will be needed. The Agency referred the sponsor to the Nasal Spray guidance for information regarding the extent of recommended characterization and performance data for each drug product under study.

MedPointe plans to conduct a 12 month study and follow the ICH guidance documents but questioned the need for a placebo arm. The FDA commented that an intranasal steroid-antihistamine product is a novel combination and raises particular safety concerns. For example, the fixed dose of fluticasone in the combination product does not permit dose titration as is recommended with the commercially available fluticasone product and may result in over-medication. Also, interactions between fluticasone and azelastine may lead to local toxicities. Without a placebo arm, any observed toxicities will be attributed to the combination product. Further discussion regarding the inclusion of placebo arm in long-term safety studies are best deferred until MedPointe has additional information about the formulation to be used, including systemic exposure to fluticasone.

MedPointe stated that they plan to do ophthalmic examinations and HPA assessments, as well as collect pharmacokinetic data for the proposed combination product. The FDA indicated that adequate assessment of HPA axis would be necessary for product labeling.

The FDA commented that blinding will be an issue in the clinical studies, given the distinctive bitter taste associated with azelastine. The adequacy of blinding is especially relevant for a factorial design study intended to demonstrate the contribution of each of the components to the proposed combination product. The FDA indicated that this blinding issue would be a problem with the development program because the proposed combination product will need to demonstrate statistical superiority over the individual components for the claimed effect in the appropriate patient population. MedPointe will need to ensure that patients are not receiving unnecessary medication if a single component is effective for them.

MedPointe stated that the intended population for the combination product is patients with inadequate control of rhinitis symptoms with monotherapy, as reflected by their TNSS scores. The FDA noted that identifying patients who have failed adequate trials of both azelastine and fluticasone, but who benefit from the combination, may prove to be difficult. Similarly, accurate description of the intended patient population in the product label will pose an additional challenge.

Reference ID: 3127881

The FDA suggested performing a pilot study with the specially formulated active and placebo comparators using the same delivery device and spray volumes. Based on the results of such a pilot study, MedPointe can better assess the promise of the proposed combination product before committing to a full-scale development program.

At the conclusion of the discussion, MedPointe summarized their understanding of the following points:

- No comparability of the proposed combination product needed to be demonstrated to the commercially available monotherapies, Flonase or Astelin®.
- Conducting a 12-month study without placebo would be their choice and risk.
- There are potential blinding concerns involving taste/smell.
- No superiority claim can be made to Flonase or Astelin®. A superiority claim of the proposed combination product can only be to the monocomparators in their study, if the data shows statistical significance.
- Identification of a patient population is of concern because the label will need to indicate how to prescribe the product.

The FDA questioned MedPointe regarding their timeframe for initiating the proposed study. MedPointe responded that they plan to begin the study in spring of 2008. The FDA acknowledged that the development program was large; therefore if a pilot study is planned, it was recommended that the data be submitted for review and discussed at the End-of-Phase 2 meeting prior to conducting a larger study.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Reference ID: 3127881

Drafted by: Bowen/September 14, 2007

Initialed by: Qiu/September 24, 2007
Seymour/September 24, 2007
Limb/September 24, 2007
Al Hakim/September 25, 2007
Peri/September 25, 2007
Sun/October 2, 2007
Wu/October 2, 2007
Chowdhury/October 3, 2007

Finalized by: Bowen/October 4, 2007

Reference ID: 3127881

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/s/

Philantha M Bowen
10/4/2007 09:31:26 AM

MEMORANDUM OF TELECON

DATE: June 25, 2007

APPLICATION NUMBER: IND 77,363

BETWEEN:

Name: Micheal I. Bernhard, Ph.D., Sr. Director Regulatory Affairs

Richard Spivey, Ph.D., Pharm.D., Sr. Vice-President Research and Development

Harry Sacks, M.D., Vice-President Medical and Scientific Affairs

Alex D'Addio, Ph.D., Vice-President Product Development

Richard Fosko, Director Regulatory Affairs

Phone: 1-888-244-5078; (b) (4)

Representing: MedPointe Pharmaceuticals

AND

Name: Sally Seymour, MD, Clinical Team Leader, Division of Pulmonary and Allergy Products

Philantha M. Bowen, MPH, RN, Regulatory Project Manger, Division of Pulmonary and Allergy Products

Colette Jackson, Regulatory Health Project Manager, Division of Pulmonary and Allergy Products

SUBJECT: Clarification of May 21, 2007, Clinical Comment Fax

Background

The FDA sent clinical comments to the sponsor regarding IND 77, 363, Azelastine-Fluticasone Combination Nasal Spray on May 21, 2007. MedPointe requested to have a teleconference to gain clarification and an understanding of the FDAs' recommendations pertaining to their clinical development plan. FDA's comments are reproduced below in **bold-face** and the discussion follows in regular font.

FDA Comments

We have the following comments regarding your clinical development program:

a. We remind you that the program will need to establish the contribution of each component to the overall efficacy of the combination drug product. Astelin Nasal Spray and Flonase Nasal Spray are not appropriate comparators because there are pharmaceutical differences between your combination drug product and these proposed comparators. The pharmaceutical differences include the use of glycerol as an excipient in your combination product, which is not present in either Flonase Nasal Spray or Astelin Nasal Spray.

Discussion:

The FDA stated that the proposed combination product will have distinct and unique pharmaceutic properties, including the excipients and preparation (micronization), which will contribute to pharmaceutic differences between the combination product and the marketed products, Flonase and Astelin. Therefore, Flonase and Astelin cannot be the comparator monotherapies. The FDA recommended that the monotherapy arms be the exact same as the combination product minus one of the drug substances. Typically, the excipients in the proposed combination product are present in the monotherapy comparators. MedPointe questioned whether the concern with glycerol was safety or efficacy. The FDA responded primarily safety, but also efficacy. The excipients can affect the properties of the nasal spray and thus, the efficacy.

The sponsor questioned how they should proceed in order to characterize the safety of glycerol. The FDA responded that MedPointe should put together a proposal and submit to the Agency for review or request a meeting.

MedPointe questioned whether they could use Flonase as an active comparator in the long-term safety study. The FDA responded that this may be a reasonable approach, but this is a preliminary comment. The FDA recommended that MedPointe include this question in the package they plan to submit.

b. In addition, the micronization of fluticasone can affect its pharmaceutical and pharmacologic properties; therefore, the use of Flonase Nasal Spray as a comparator is not appropriate. Your clinical development program will need to address these issues.

Discussion

MedPointe stated that Flonase was an appropriate comparator, citing that the API is currently used in an approved ANDA. Thus, micronization of fluticasone should not have any effect on the pharmacologic properties because bioeqvialence has been established to the Flonase product. In addition, the sponsor stated that the current, available marketed product should be compared to the proposed combination drug product, because using a different comparator may be unclear to prescribing physicians.

The FDA responded that the micronizaton process for the fluticasone monotherapy needs to be the same micronization as in the proposed combination product. Micronization may affect various properties of the drug substance, including particle size distribution. Therefore it can not be assumed that the proposed combination product will have the same pharmaceutic properties as Flonase. If MedPointe has data to support that the micronization of fluticasone in their combination product is the same as in Flonase, they should submit this information in the briefing package. In addition, the FDA stated that the combination product and Flonase utilize two separate devices. Typically, the same device is used for the comparator monotherapies and the proposed combination product.

MedPointe stated that they believe that Flonase is an appropriate comparator. In addition, they wish to discuss a proposal to support the safety of glycerol. The FDA recommended they submit their proposal with rationale and any data to support their arguments and request a meeting for further discussion.

Additional Discussion

MedPointe plans to conduct initial studies in adults and children age 12 and over. If efficacy and safety is established in adults, then pediatric studies would follow. The sponsor plans to submit an NDA with data for adults followed by a supplement with pediatric data. The FDA responded that this approach was acceptable.

Philantha M. Bowen, MPH, RN
Sr. Regulatory Project Management Officer

Drafted: Bowen/ June 27, 2007
Initialed: Jackson/ July 3, 2007; Seymour/July 5, 2007
Finalized: Bowen/July 5, 2007

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/s/

Philantha M Bowen
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CSO