

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022522Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22522

SUPPL #

HFD #

Trade Name DALIRESP

Generic Name Roflumilast

Applicant Name Forest Research Institute, Inc.

Approval Date, If Known February 28, 2011

### 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)(1)

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:

d) Did the applicant request exclusivity?

YES  NO

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

5 Years per 21 CFR 314.50 (j) and 21 CFR 314.108(b)(2)

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?

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#

NDA#

NDA#

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 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:

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

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

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



Investigation #2

!

!

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: Carol Hill, M.S.

Title: Regulatory Health Project Manager, Division of Pulmonary, Allergy, and Rheumatology Products

Date: February 4, 2011

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.

Title: Director, Division of Pulmonary, Allergy, and Rheumatology Products

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

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/s/  
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CAROL F HILL  
02/28/2011

BADRUL A CHOWDHURY  
02/28/2011

9/11/2009



Roflumilast

(2.0)

1 of 1

## DEBARMENT CERTIFICATION

NDA No: 22-522

**Daxas (roflumilast tablets)**

for the treatment of Chronic Obstructive Pulmonary Disease (COPD)

Pursuant to provision of 21 U.S.C. 335a(k)(1), PPD Development LP, through Kevin Johnson, and Nycomed GmbH, through Christoph Bunte, 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.

Date: 08 September 2009

A handwritten signature in black ink, appearing to read "KBJ", written over a horizontal line.

Kevin B. Johnson, PhD  
Associate Director  
US Regulatory Affairs  
PPD Development, LP

A handwritten signature in black ink, appearing to read "C. Bunte", written over a horizontal line.

Christoph Bunte, PhD  
Senior Regulatory Affairs Manager  
Regulatory Product Development  
Nycomed GmbH

7/17/2009



**DEBARMENT CERTIFICATION**

NDA No: 22-522

**Daxas (roflumilast tablets)**  
for the treatment of Chronic Obstructive Pulmonary Disease (COPD)

Pursuant to provision of 21 U.S.C. 335a(k)(1), Nycomed GmbH, through Dr. Susanne Heiland-Kunath and Dr. Christoph Bunte, hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) 21 U.S.C 335a(a) or (b) of the Generic Drug enforcement Act of 1992, in connection with the above referenced application.

Date: 08 April 2009

  
i.V. Dr. Susanne Heiland-Kunath  
Director  
Regulatory Product Development

  
i.V. Dr. Christoph Bunte  
Senior Regulatory Affairs Manager  
Regulatory Product Development



NDA 022522

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Forest Research Institute, Inc.  
Harborside Financial Center  
Plaza 5, Suite 1900  
Jersey City, New Jersey 07311

ATTENTION: Lisa L. Travis, M.S., RAC  
Director, Regulatory Affairs

Dear Ms. Travis:

Please refer to your New Drug Application (NDA) dated July 15, 2009, received July 17, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Roflumilast Tablets, 500 mcg.

We also refer to your February 15, 2011, correspondence, received February 15, 2011, as amended February 25, 2011 requesting review of your proposed proprietary name, Daliresp. We have completed our review of the proposed proprietary name, Daliresp and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 25, 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, Carol Hill at (301) 796-1226.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
02/28/2011



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: February 24, 2011**

<b>To: Kevin McDonald</b> Associate Director, Regulatory Affairs	<b>From: Carol Hill, M.S.</b> Regulatory Health Project Manager carol.hill@fda.hhs.gov
<b>Company: Forest Research Institute, Inc.</b>	<b>Division of Pulmonary, Allergy, and Rheumatology Products</b>
<b>Fax number: 201-524-9711</b>	<b>Fax number: 301-796-9728</b>
<b>Phone number: 201-427-8232</b>	<b>Phone number: 301-796-1226</b>
<b>Subject: NDA 22522 – Labeling Revisions: Package Insert and Medication Guide</b>	

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**Total no. of pages including cover: 23**

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**Comments: Please acknowledge receipt.**

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**Document to be mailed:             YES             NO**

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NDA 22522  
Forest Research Institute, Inc.  
Roflumilast

Per your submission dated, February 22, 2011, we are providing our comments regarding your revised label. We have also included the Agency's revisions for the Medication Guide (MG). Please see the following comments below, the attached package insert and MG. In the attached revised package insert labeling, insertions are underlined and deletions are strike-out. Provide updated labeling to include the comments below and the revisions shown in the attached package insert and MG.

The following are comments pertaining to the HIGHLIGHTS section of the product label:

### DRUG INTERACTIONS

(b) (4)

The following are comments pertaining to the FULL PRESCRIBING SECTION of the product label:

### ADVERSE REACTIONS

Line 153. The <sup>(b) (4)</sup> language was removed. Even one serious adverse reaction can be important so the incidence, which is usually low, can be misleading.

### CLINICAL PHARMACOLOGY

Section 12.3. The legend was removed from Figure 1 and replaced with separate text with minor edits for clarity. This will also allow for easier insertion of the TRADENAME when decided upon

The following comments pertain to the changes in your MG. Changes to your proposed MG have been made to:

- simplify wording and clarify concepts where possible
- ensure that the MG is consistent with the prescribing information (PI)
- remove unnecessary or redundant information within the MG
- ensure that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Note that due to extensive edits the required changes in the MG are not tracked. However, there are two FDA comments that are highlighted in the MG.

In addition, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for*

*Prescription Labeling and Consumer Medication Information for People with Vision Loss.* The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

If you have questions, contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

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

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/s/  
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CAROL F HILL  
02/24/2011



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary, Allergy, and  
Rheumatology Products**

### **Memorandum of Facsimile Correspondence**

Date: February 18, 2011

To: Kevin McDonald, Associate Director, Regulatory Affairs

Company: Forest Research Institute, Inc.

Fax: 201-524-9711

Phone: 201-427-8232

From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary, Allergy and Rheumatology Products

Subject: NDA 22-522 – Labeling Comments and information request

# of Pages: 17

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Thank you.

[carol.hill@fda.hhs.gov](mailto:carol.hill@fda.hhs.gov)

NDA 22522  
Forest Research Institute, Inc.  
Roflumilast

In response to your submission dated, February 11, 2011 and our teleconference dated, February 14, 2011, we have the following labeling comments and requests for information. Be advised that the Medication Guide revisions and additional comments will be forthcoming as we continue to review the labeling.

Section 4 Contraindications:

[Redacted] (b) (4)

Section 8.5 Geriatric Use, line 273 and Section 14.1 COPD, line 483:

- Clarify patient numbers. In section 14, it states that 4425 patients with COPD received TRADENAME, while in section 8, the number is 4438.

Section 12.3, Pharmacokinetics, subsection, Race:

- Additional comments will be provided after the numbers are verified.

If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

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/s/  
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CAROL F HILL  
02/18/2011



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: February 14, 2011**

<b>To:</b> Kevin McDonald Associate Director, Regulatory Affairs	<b>From:</b> Carol Hill, M.S. Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute	Division of Pulmonary, Allergy and Rheumatology Drug Products
<b>Fax number:</b> 201-524-9711	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-427-8232	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 22522 - Roflumilast Post-Marketing Commitment Information Request

**Total no. of pages including cover:** 2

**Comments:** Please acknowledge receipt

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NDA 22522  
Forest Research Institute, Inc.  
Roflumilast 500 mcg Tablet

Your submission dated August 30, 2010, to NDA 22-522, is currently under review. We have the following comments or request(s) for information:

We refer you to the teleconference on January 20, 2011, during which we discussed post-marketing commitments for your roflumilast COPD program and agreed in principal that you would conduct the following study as a post-marketing commitment in the United States:

- Conduct a controlled clinical study to evaluate the efficacy of roflumilast as an add-on therapy to a long-acting beta agonist and inhaled corticosteroid fixed dose combination therapy in the population of COPD patients for which roflumilast is indicated [severe COPD (FEV1 < 50% predicted) associated with chronic bronchitis and a history of exacerbations]. The design of the study should be appropriate to demonstrate a clinically relevant beneficial effect of roflumilast as an add-on therapy compared to a long-acting beta agonist and inhaled corticosteroid fixed dose combination treatment.

We request a response to this request for you to conduct the clinical study outlined above as a post-marketing commitment. In your response, provide specific timelines for final protocol submission, study completion date, and final report submission. Please provide your response by COB on February 26, 2011.

If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-2226.

Drafted by: Durmowicz/February 11, 2011  
Seymour/February 11, 2011  
Barnes/February 14, 2011  
Finalized: chill/February 14, 2011

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/s/  
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CAROL F HILL  
02/14/2011



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary, Allergy, and  
Rheumatology Products**

**Memorandum of Facsimile Correspondence**

Date: February 11, 2011  
To: Kevin McDonald, Associate Director, Regulatory Affairs  
Company: Forest Research Institute, Inc.  
Fax: 201-524-9711  
Phone: 201-427-8232  
From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary, Allergy and Rheumatology Products

Subject: NDA 22522 - REMS Information Request  
# of Pages: 9

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Thank you.  
[carol.hill@fda.hhs.gov](mailto:carol.hill@fda.hhs.gov)

NDA 22522  
Forest Research Institute, Inc.  
Roflumilast

Your resubmitted NDA dated August 30, 2010, received August 31, 2010, for roflumilast, 500 mcg tablets is currently under review. The enclosed Risk Evaluation and Mitigation Strategy (REMS) document contains clarification comments for some of the changes made to the proposed REMS. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments as we continue our review. Submit revised REMS to include the recommendations listed below and incorporating changes shown in the attached marked up REMS by COB February 15, 2011.

If there are any questions, contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Enclosure: Recommendations to the REMS

The following comment pertains to the REMS GOAL:

a. **GOAL**

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of roflumilast tablets.

- b. Your Medication Guide distribution plan appears to be acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document. See our editorial comments on this section of the proposed REMS (see Appendix A)
- We remind you that under 21 CFR 208.24, you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. You state that you plan to make tear pads containing the Medication Guide available to pharmacies for direct distribution to patients. We find this distribution plan acceptable.
  - We remind you that under 21 CFR 208.24, you are responsible for ensuring that the roflumilast tablet carton or container label contains a prominent statement that the Medication Guide should be dispensed to each patient. We suggest the following language if the product is enclosed in the carton. "Dispense accompanying Medication Guide to each patient."
- c. Your proposed timetable for submission of assessments (18 months, 3 years and 7 years) is acceptable.

We have the following editorial comments regarding the REMS.

- Regarding your REMS Assessment Plan, the submitted methodology lacks sufficient detail to complete a review.

1. Submit for review the detailed plan that will be used to evaluate patients' understanding about the risks associated with and safe use of [Tradename]. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." If the plan is to conduct the required assessment using a survey, the submission should include all methodology and instruments that will be used to evaluate the patients' knowledge about the risks associated with and safe use of [Tradename].
2. We encourage you to recruit respondents using a multi-modal approach. For example, patients could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.  
Explain how often non-respondent follow-up or reminders will be completed.  
Explain how an incentive or honorarium will be offered, and the intended amount.  
Explain how recruitment sites will be selected.  
Submit for review any recruitment advertisements.
3. Define the sample size and confidence intervals associated with that sample size.
4. Define the expected number of patients to be surveyed to obtain the final proposed sample size, and how the sample will be determined (selection criteria)
5. The patient sample should be demographically representative of the patients who use [Tradename].  
If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography.
6. Explain the inclusion criteria; that is, who is an eligible respondent. For example, *patient* respondents might be:
  - Age 18 or older
  - Currently taking [Tradename] or have taken in past 3 months
  - Not currently participating in a clinical trial involving [Tradename]
  - Not a healthcare providerSubmit any screener instruments, and describe if any quotas of sub-populations will be used.
7. Explain how surveys will be administered, and the intended frequency.  
We encourage you to offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, or in person.  
Explain how surveyors will be trained.
8. Explain controls used to compensate for the limitations or bias associated with the methodology.
9. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.  
Potential respondents should be told that their answers will not affect their ability to receive or take [Tradename], and that their answers and personal information will be kept confidential and anonymous.
10. Respondents should not be eligible for more than one wave of the survey.

11. The assessment is to evaluate the effectiveness of the REMS in achieving the REMS goal by evaluating patients' knowledge of the serious risks associated with use of [Tradename]. The assessment is not to evaluate consumer comprehension of the Medication Guide.  
Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
13. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.  
Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about [Tradename]?" section of the Medication Guide. The questions should be about understanding the risk, the symptoms, and what to do if the event occurs. The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.  
The order of the multiple choice responses should be randomized on each survey.
14. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.  
Respondents should not have the opportunity or ability to go back to previous questions in the survey.  
Explain if and when any education will be offered for incorrect responses.
15. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
16. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,  
*Now we are going to ask you some questions about the Medication Guide you may have received with [Tradename]. The Medication Guide is a paper handout that contains important information about the risks associated with use of [Tradename] and how to use [Tradename] safely. Medication Guides always include the title "Medication Guide" followed by the word [Tradename] and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about [Tradename]," "What is [Tradename]," and "Who should not take [Tradename]."*
17. Use the following (or similar) questions to assess receipt and use of the Medication Guide.
  - Who gave you the Medication Guide for [Tradename]? (Select all that apply)
    - a) My doctor or someone in my doctor's office
    - b) My pharmacist or someone at the pharmacy
    - c) Someone else - please explain: \_\_\_\_\_
    - d) I did not get a Medication Guide for [Tradename]

- Did you read the Medication Guide?
    - All,
    - Most,
    - Some,
    - None
  - Did you understand what you read in the Medication Guide?
    - All,
    - Most,
    - Some,
    - None
  - Did someone offer to explain to you the information in the Medication Guide?
    - Yes, my doctor or someone in my doctor's office
    - Yes, my pharmacist or someone at the pharmacy
    - Yes, someone else – please explain: \_\_\_\_\_
    - No
  - Did you accept the offer? Yes or No
  - Did you understand the explanation that was given to you?
    - All,
    - Most,
    - Some,
    - None
  - Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA
18. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
19. Data may be stratified by any relevant demographic variable, and also presented in aggregate. We encourage you to submit with your assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

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

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/s/  
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CAROL F HILL  
02/11/2011

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF PULMONARY AND ALLERGY PRODUCTS

**DATE:** February 7, 2011

**TO:** NDA 22522

**FROM:** Carol Hill, M.S., Regulatory Health Project Manager

**SUBJECT:** Summary of telephone conversations with Forest provide update regarding the status of the application review and to discuss PMCs/PMRs.

### SUMMARIES

#### **December 22, 2010 Teleconference**

##### Forest Research Institute Attendees

Lisa Travis  
June Bray  
Christoff Brunta  
Kevin McDonald

##### Division of Pulmonary, Allergy, and Rheumatology Products Attendees

Anthony Durmowicz, M.D., Clinical Team Leader, CDTL for review of NDA 2252  
Carol Hill, M.S., Regulatory Health Project Manager

##### Discussion:

Forest was informed that the focal point of the conversation was to continue our open forum of communication per our 21<sup>st</sup> Century Review guidelines by providing an update to the of the review of the application. Dr. Durmowicz stated that recommendations for action were not available because the review was ongoing. Forest was alerted that initially labeling will be sent as sections so that we could potentially come to agreement on sections of the label earlier than others. Dr. Durmowicz stated that the review of the CMC portions of the application was complete and noted that agreement has been met by Forest and the CMC review team regarding labeling revisions. Forest inquired if the Agency could provide feedback regarding the REMS program. Dr. Durmowicz stated that the safety review for roflumilast was ongoing and that discussion of a REMS would be provided later in the review cycle.

## **January 20, 2011 Teleconference**

### Forest Research Institute Attendees

Dr. Lawrence Bassin, Executive Director, Pharmacovigilance and Risk Mgmt  
Dr. Mariette Boerstoeel, Chief Safety Officer, Vice President Global Drug Safety  
Dr. Dawn Boykin, Senior Scientist, Clinical Development -Respiratory  
June Bray, Vice President, Regulatory Affairs  
Dr. Joseph Camardo, Sr. Vice President, Respiratory and Medical Affairs  
Dr. Parviz Ghahramani, Executive Director, Clinical Pharmacokinetics & Drug Dynamics  
Dr. Kim Li, Sr Director - Pharmacovigilance and Risk Management  
Kevin McDonald, Associate Director, Regulatory Affairs  
Puneet Sachdev, Associate Director, Project Management  
Lisa Travis, Director, Regulatory Affairs  
Dr. Hongjie Zheng, Executive Director, Biostatistics  
Dr. Haiyuan Zhu, Associate Director, Biostatistics

### Nycomed Attendees:

Dr. Eva Ammon, Project Management  
Dr. Susanne Heiland-Kunath, Director, Regulatory Product Development  
Dr. Soeren Kristiansen, Sr. Director, Data Science  
Dr. Gezim Lahu, Head, Clinical Pharmacokinetics & Drug Dynamics  
Dr. Hans Mosberg, Director, Medical Safety Evaluation  
Dr. Sabin Obert, Sr. Medical Expert

### Division of Pulmonary, Allergy, and Rheumatology Products Attendees

Anthony Durmowicz, M.D., Clinical Team Leader, CDTL for review of NDA 22522  
Sally Seymour, M.D., Deputy Director for Safety  
Carol Hill, M.S., Regulatory Health Project Manager

## DISCUSSION

### Post-Marketing Commitments:

The purpose of the teleconference was to begin discussion regarding the post-marketing commitments that we would ask Forest to agree to which included a study to assess the benefit of roflumilast as an add-on therapy to a fixed dose LABA/ICS combination drug. Forest was told that this study would be similar in nature to the study which Nycomed agreed to as a PMC when roflumilast was approved in the EU in June, 2010. Forest should discuss the PMC internally and propose dates for when the final protocol would be submitted, dated for completion of the study and when the final study report would be submitted. The Agency stated that, regarding the date for final protocol submission, Forest should build in adequate time for back and for the discussion prior to the submission of the final protocol.

In response to the Agency's request for Forest to provide information on roflumilast post-marketing studies and commitments in Europe, Forest sent a list of Post Authorization Commitments (PACs) requested by the CHMP that Nycomed has agreed to undertake with

further details on the studies planned to fulfill these commitments (see attached correspondence dated, January 11, 2011). In the correspondence, Forest committed to conduct a long-term comparative observational safety study. The Agency asked Forest to provide clarification regarding the observational study. Forest stated that it is a longer term safety study, an epidemiological approach to evaluate mortality including cardiovascular, suicide and cancer deaths rates. At the Agency's request to provide further information to assist in determining its usefulness for a US post-marketing study, Forest indicated that the study is still under discussion with no fixed protocols or outlines and that the study's limitation is that of a large database. Forest also noted that the formulation used in the EU is different. Since the formulations are different, the Agency inquired would the study address FDA's concerns regarding the clinical trials. Forest stated that they would have more than one clinical trial with clinically meaningful endpoints and thus satisfy US requirements. Forest asked if the Agency has specific thoughts regarding the observational study. The Agency commented that we would need to discuss any potential benefits of an observational study internally before any decision on whether it would be a PMC could be made.

Labeling:

Dr. Durmowicz stated that Clinical Pharmacology and Clinical Sections of the label will be provided on today for the January 21, 2010 labeling teleconference with Forest.

Drafted by: Chill/January 31, 2011  
Clearance History: Durmowicz/February 3, 2011  
Finalized: Chill/February 7, 2011

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/s/  
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CAROL F HILL  
02/07/2011



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy Products**

### **Memorandum of Facsimile Correspondence**

Date: February 2, 2011  
To: Kevin McDonald, Associate Director, Regulatory Affairs  
Company: Forest Research Institute, Inc.  
Fax: 201-524-9711  
Phone: 201-427-8232  
From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary, Allergy and Rheumatology Products

Subject: Labeling revisions for the entire label re: NDA 22-522

# of Pages: 26

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Thank you.

[carol.hill@fda.hhs.gov](mailto:carol.hill@fda.hhs.gov)

NDA 22522

Forest Research Institute, Inc.

Roflumilast

Per our email correspondence dated, January 31, 2011, we are providing our revisions of the entire label. In that correspondence, we informed you that some of the patient data would have to be updated. For the purposes of labeling, the data presented should reflect the population in which roflumilast was determined to be efficacious and have an adequate safety profile. As such, in CLINICAL STUDIES, Section 14.1, we have listed that data from 8 clinical trials (FK1-101, M2-107, M2-111, M2-112, M2-124, M2-125, M2-127, and M2-128) formed the basis from which the determination of the safety and efficacy of roflumilast was primarily made. As a result, applicable demographic, patient number, and adverse reaction data in several sections of the label will need to be revised. Please recalculate and insert the appropriate values in the sections of the label designated below and supply summary data to support the changes. Additionally, please check any values FDA has edited and, if different than the values you calculate, supply justification for a change.

In the attached revised package insert labeling, insertions are underlined and deletions are strike-out. We have also included additional comments regarding specific sections of the label.

### **Warnings and Precautions**

Section 5.2: Insert the appropriate numbers derived from the data from clinical trials FK1-101, M2-107, M2-111, M2-112, M2-124, M2-125, M2-127, and M2-128 in the appropriate areas designated by “X” or “N” (for number).

Section 5.3: Again, insert the appropriate values based on data from the 8 clinical trials listed above.

### **Adverse Reactions**

- Section 6.1
  - Insert appropriate patient number values designated by “X” based on the 8 clinical trials.
  - Lines 318-320: Modify the list of serious adverse reactions based on recalculated data from the 8 trials.
  - Table 1 “Adverse Reactions Reported by  $\geq 2\%$  of Patients Treated with TRADENAME and Greater than Placebo”: Supply per cent and number of adverse reactions based on the 8 trials (see example in the label text). Per cent should be rounded to the nearest whole number. If less than one per cent use “<1”.
  - Lines 333-334: Insert appropriate adverse reactions grouped by system organ class.
- Section 6.2
  - If significant post-marketing adverse reaction data are available from countries where roflumilast is approved for use in COPD patients, they should be added as Section 6.2.

### **Use in Specific Populations**

- Section 8.5

- Insert appropriate patient number values designated by “X” based on the 8 clinical trials.

In addition, note that the Medication Guide is currently being reviewed and edits will be forthcoming.

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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

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/s/  
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CAROL F HILL  
02/02/2011



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** January 21, 2011

<b>To:</b> Kevin M. McDonald Associate Director, Regulatory Affairs	<b>From:</b> Carol Hill, M.S. Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute, Inc.	Division of Pulmonary, Allergy and Rheumatology Products
<b>Email Address:</b> kevin.mcdonald@frx.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-427-8232	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 22522 – CMC request regarding prior agreement dated Jan. 22, 2010

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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NDA 22522  
Forest Research Institute  
Roflumilast

Please refer to your January 22, 2010 submission in response to comment #4 of our January 11, 2010 correspondence.

Regarding the agreement to revisit the drug substance particle size distribution acceptance criteria provided in the January 22, 2010, amendment, specify the expected number of batches that will be used to finalize the criteria and provide a date by which the revision will be finalized and reported to the Agency.

If there are any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted by: CHill/January 6, 2010  
Clearance History: Barnes/January 21, 2011  
Bertha/January 5, 2011  
Peri/January 5, 2011  
Finalized: CHill/January 21, 2011

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/s/  
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CAROL F HILL  
01/21/2011



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy Products**

**Memorandum of Facsimile Correspondence**

Date: January 12, 2010

To: Kevin McDonald, Associate Director, Regulatory Affairs

Company: Forest Research Institute, Inc.

Fax: 201-524-9711

Email: kevin.mcdonald@frx.com

Phone: 201-427-8232

From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary, Allergy and Rheumatology Products

Subject: Labeling Revisions and Comments re: NDA 22-5222

# of Pages:

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Thank you.  
**carol.hill@fda.hhs.gov**

NDA 22522  
Forest Research Institute, Inc.  
Roflumilast

We have begun our review of the label in your October 29, 2010 submission. Per our conversation on December 22, 2010, be advised that additional labeling comments will be forthcoming as we continue to review the labeling. Since we will be providing our revisions and comments to specific sections of the labeling, we do not expect you to provide revised labeling at present. However, if you have questions regarding any of the revised sections, we request that you forward your comments so that we may address any issues you may have. We have included comments regarding carton and container labeling.

1. The following is a general comment for all labels and labeling:

Delete or minimize the triangular graphic design from the position following the proprietary name because it is as prominent as the proprietary name, established name, and strength. The proprietary name, established name, and strength should be the most prominent information communicated on the principle display panel.

2. The following pertains to the container labels (30 count and 90 count) and professional sample container label (30 count):

Relocate the net quantity statement (30 tablets or 90 tablets) away from the product strength to improve readability and decrease the potential for confusion with the product strength (500 micrograms). We suggest moving the net quantity statement to the bottom of the principle display panel.

3. The following pertains to the professional sample blister pack label (7 count):

The label containing the proprietary name, established name, strength and other information is present over the entire back panel. Thus when tablets are removed this information may be destroyed and unreadable. The proprietary name, established name, strength, lot number and expiration date should appear on the back of every blister that contains a tablet, so that the information is immediately available if the card is cut to separate a dose from the rest of the blister pack.

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

Drafted by: chill/January 10, 2011  
Clearance History: Barnes/January 11, 2011  
                    Bertha/January 7, 2011  
                    Peri/January 7, 2011  
                    Durmowicz/January 7, 2011  
Finalized: January 13, 2011

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/s/  
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CAROL F HILL  
01/13/2011



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy Products**

**Memorandum of Facsimile Correspondence**

Date: January 10, 2011

To: Kevin McDonald, Associate Director, Regulatory Affairs

Company: Forest Research Institute, Inc.

Fax: 201-524-9711

Email: kevin.mcdonald@frx.com

Phone: 201-427-8232

From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary, Allergy and Rheumatology Products

Subject: Labeling Revisions and Comments re: NDA 22-5222

# of Pages: 7

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Thank you.  
**carol.hill@fda.hhs.gov**

NDA 22522  
Forest Research Institute, Inc.  
Roflumilast

We have begun our review of the label in your October 29, 2010 submission. Per our conversation on December 22, 2010, be advised that additional labeling comments will be forthcoming as we continue to review the labeling. Since we will be providing our revisions and comments to specific sections of the labeling, we do not expect you to provide revised labeling at present. However, if you have questions regarding any of the revised sections, we request that you forward your comments so that we may address any issues you may have. In the attached revised package insert labeling, insertions are underlined and deletions are strike-out. We have also included comments regarding formatting.

1. The following comments pertain to the HIGHLIGHTS section of the product label:
  - a. Highlights, excluding the boxed warning, must be limited in length to one-half page.
  - b. Line 12, INDICATIONS AND USAGE section, omit the additional space between the words daily and treatment.
  - c. Line 36, WARNINGS AND PRECAUTIONS section, insert the word with between treatment and Daxas.
2. The following comments pertain to the FULL PRESCRIBING INFORMATION: CONTENTS (TOC) section of the product label:
  - a. Do not include the medication guide as a subsection heading.
3. The following comments pertain to the FULL PRESCRIBING INFORMATION section of the product label:
  - a. Line 202, ADVERSE REACTIONS section, insert the word “clinical” after the words may not reflect the rates observed in ..... practice.
  - b. Line 857, remove Medication Guide revised XXXXXX.
  - c. Line 861, remove Rx only.

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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CAROL F HILL  
01/10/2011

## MEMORANDUM

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

**DATE:** December 27, 2010

**FROM:** Carol Hill, Regulatory Health Project Manager, DPARP

**SUBJECT: Clarification regarding Clinical Pharmacology Information Request Dated, December 6, 2010**

**APPLICATION/DRUG: NDA 22522/Roflumilast**

### **Attendees:**

#### **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**

Anthony Durmowicz, MD, Clinical Team Leader  
Yun Xu, Ph.D., Clinical Pharmacology Team Leader  
Ping Ji, Ph.D., Clinical Pharmacology Reviewer

#### **Forest Research Institute, Inc:**

Parviz Ghahramani, Clinical Pharmacology and Drug Dynamics  
Andreas Grill, Pharmaceutical Research and Development  
Susanne Heiland-Kunath, Regulatory – Nycomed  
Abhijeet Jakate, Clinical Pharmacology and Drug Dynamics  
Gezim Lahu, Clinical Pharmacology and Drug Dynamics – Nycomed  
Shashank Mahashabde, Pharmaceutical Research and Development  
Kevin McDonald, Regulatory  
Puneet, Sachdev, Project Management  
Lisa Travis, Regulatory

### **BACKGROUND**

A request was sent to Forest Research Institute, Inc. on December 6, 2010 to request additional information to facilitate the review of the September 10, 2010, Class 2 Resubmission of NDA 22522. Forest acknowledged receipt of the request via email on December 9, 2010 and requested a brief teleconference with the clinical pharmacology team to clarify what data would be needed to satisfy the request. The requested information is shown below in bold italics and Forest's email response for clarification is in italics. The Clinical Pharmacology Response is in normal font.

**December 6, 2010 Clinical Pharmacology Information Request**

***To assess the P-gp substrate liability of roflumilast-N-oxide, submit data that determines if roflumilast-N-oxide is a P-gp substrate.***

*Forest's Response dated, December 9, 2010:*

*Please find the following background information in support of the proposed teleconference that may address the question raised by the reviewer:*

*Study FHP027 (Study 208/2001), submitted in NDA 22-522 in Module 5.3.3.4, was a drug interaction study in human healthy subjects that was designed to fully characterize the effect of both roflumilast and roflumilast N-oxide on digoxin. The results from this drug-interaction study showed that neither roflumilast nor roflumilast n-oxide is a P-gp substrate.*

*Study FHP027 was conducted in healthy human subjects and investigated the effect of co-administration of digoxin and steady-state roflumilast. PK levels of roflumilast, roflumilast N-oxide, and digoxin were measured. The ratio of geometric means for  $AUC_{0-24hr}$  and  $C_{max}$  for roflumilast, roflumilast N-oxide and digoxin are presented in Table 1 below:*

***Table 1: Ratio of Geometric Means for Co-administration of Digoxin with steady state roflumilast (Test) versus roflumilast or Digoxin Alone (Reference)***

<b><i>PK Parameter</i></b>	<b><i>Roflumilast</i></b>	<b><i>Roflumilast N-Oxide</i></b>	<b><i>Digoxin</i></b>
<b><i><math>AUC_{0-24hr}</math></i></b>	<b><i>101 (96-107)</i></b>	<b><i>97 (92-102)</i></b>	<b><i>101 (92-111)*</i></b>
<b><i><math>C_{max}</math></i></b>	<b><i>95 (80-113)</i></b>	<b><i>90 (84-96)</i></b>	<b><i>115 (99-134)</i></b>

*\*  $AUC_{0-inf}$*

*Relevant tables from Module 2.7.2 Summary of Clinical Pharmacology describing the study design, pharmacokinetic data and ratios of geometric means from this study (Section 2.7.2.2.3.1.7) are provided as an attachment to this Email.*

*As seen from these ratios, there was no impact of digoxin on the steady-state PK of roflumilast or roflumilast N-oxide. Also, in the presence of roflumilast and roflumilast N-oxide, there was no significant impact on plasma digoxin concentrations. These data indicate there is no clinically relevant interaction of roflumilast or roflumilast N-oxide with digoxin and address the P-gp liability of both roflumilast and roflumilast N-oxide.*

*Given that roflumilast N-oxide is produced systemically (after absorption of roflumilast), an interaction on the absorption through the gut is unlikely for roflumilast N-oxide. Therefore, we feel that the most relevant data that can address the specific question about the effect of roflumilast N-oxide on P-gp activity has been presented in the clinical study, FHP027.*

*We would like to request this brief teleconference with the reviewer to clarify whether any additional data, apart from the data described above, is being requested by the reviewer.*

Clinical Pharmacology Response:

The Agency commented that the study presented utilizes Digoxin with roflumilast to demonstrate if Roflumilast is a P-gp inhibitor. Digoxin is a P-gp substrate. The Agency stated that another in-vitro study should be conducted using N-oxide to determine whether N-oxide is a P-gp substrate.

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/s/  
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CAROL F HILL  
01/04/2011



NDA 022522

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Forest Research Institute, Inc.  
Harborside Financial Center  
Plaza 5, Suite 1900  
Jersey City, New Jersey 07311

ATTENTION: Lisa L. Travis, MS, RAC  
Director, Regulatory Affairs

Dear Ms. Travis:

Please refer to your New Drug Application (NDA) resubmitted August 30, 2010, received August 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Roflumilast Tablets, 500 mcg.

We also refer to your September 22, 2010, correspondence, received September 22, 2010, requesting review of your proposed proprietary name, Daxas. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)



If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Carolyn Volpe, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5204. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Carol Hill at 301-796-1226.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
12/20/2010



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: December 6, 2010**

<b>To:</b> Kevin M. McDonald Associate Director, Regulatory Affairs	<b>From:</b> Carol Hill, M.S. Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Email Address:</b> kevin.mcdonald@frx.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-427-8232	<b>Phone number:</b> 301-796-2300
<b>Subject:</b> NDA 22522 – Clinical Pharmacology Information Request	

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**Total no. of pages including cover: 3**

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**Comments: Please acknowledge receipt.**

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**Document to be mailed:** YES xNO

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NDA 22522  
Forest Research Institute, Inc.  
Roflumilast

Your resubmission dated August 30, 2010, to NDA 22522, is currently under review. We have the following request for information.

To assess the P-gp substrate liability of roflumilast-N-oxide, submit data that determines if roflumilast-N-oxide is a P-gp substrate.

Submit this information before December 23, 2010. Provide this information by fax to 301-796-9728 and formally submit it to the application. If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted by: chill/December 1, 2010  
Clearance: Barnes/December 3, 2010  
            Ji/December 1, 2010  
            Xu/December 1, 2010  
Finalized: chill/December 6, 2010

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/s/  
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CAROL F HILL  
12/06/2010



**FACSIMILE TRANSMITTAL SHEET**

**DATE: October 14, 2010**

**To:**  
Lisa Travis  
Director, Regulatory Affairs

**From: Swati Patwardhan**  
Regulatory Health Project Manager  
Office of Pharmaceutical Science  
Office of New Drug Quality Assessment  
Division of New Drug Quality  
Assessment III

**Company: Forest Research Institute,  
Inc.**

**Fax number: 201-524-9711**

**Fax number: 301-796-9748**

**Phone number: 201-386-2031**

**Phone number: 301-796-4085**

**Subject: NDA 22-522**  
Request for Letter of Authorization

**Total # of pages including cover: 2**

**Comments:**

**Original document to be mailed:**

Yes

No

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.

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NDA 22-522

We are currently reviewing the CMC section of NDA 22-522. [REDACTED] (b) (4)  
[REDACTED], is listed as a contract  
micronization site for the manufacturing of the drug substance. Please obtain and submit  
a Letter of Authorization from [REDACTED] (b) (4) allowing our access to the information in  
[REDACTED] (b) (4).

Submit your response to me via telephone facsimile to 301-796-9748 or email at  
[swati.patwardhan@fda.hhs.gov](mailto:swati.patwardhan@fda.hhs.gov) by close of business on October 20, 2010. Your response  
will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Swati Patwardhan, Regulatory Project Manager,  
at 301-796-4085.

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/s/

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SWATI A PATWARDHAN  
10/14/2010

## REQUEST FOR CONSULTATION

TO (*Office/Division*): ODE I/Division of Psychiatry Products  
Attn: David Berman/RPM/301-796-2260

FROM (*Name, Office/Division, and Phone Number of Requestor*):  
ODE II/Division of Pulmonary, Allergy, and  
Rheumatology Products  
Carol Hill/RPM/301-796-1226

DATE October 13, 2010	IND NO.	NDA NO. 22522	TYPE OF DOCUMENT Resubmission of NDA	DATE OF DOCUMENT 8/31/10
NAME OF DRUG Daxas (roflumilast)		PRIORITY CONSIDERATION P	CLASSIFICATION OF DRUG PDE 4 Inhibitor	DESIRED COMPLETION DATE November 30, 2010

NAME OF FIRM: Forest Lab

### REASON FOR REQUEST

#### I. GENERAL

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

#### II. BIOMETRICS

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

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG SAFETY

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

#### V. SCIENTIFIC INVESTIGATIONS

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

**COMMENTS / SPECIAL INSTRUCTIONS:**

**Background Information:**

Psychiatric adverse events including suicides and depression were safety concerns associated with the use of roflumilast, the subject of NDA 22522. Roflumilast clinical trials enrolled over 24,000 subjects in 6 indications (COPD, asthma, allergic rhinitis, diabetes, rheumatoid and osteoarthritis). Among the 7800 COPD patients who received the active roflumilast treatment, there were 3 complete suicides and 2 suicides attempts, compared to 1 suicide ideation in a patient who received the placebo. Although there were no reported suicides (completed, attempted or ideation) from trials in other indications, there was a 2 to 3 times increase in psychiatric adverse events such as depression, anxiety and insomnia in patients who received roflumilast compared to those who received placebo in clinical trials across all 6 indications. DPARP felt that the sponsor did not fully assess the safety signal of suicides and psychiatric adverse reactions in the NDA. In the complete response letter, the sponsor was told that to “understand the signal strength and its impact on the risk benefit assessment”, a comprehensive review and evaluation of the roflumilast program data base for suicidality should be performed utilizing an acceptable method,

such as the C-CASA.

The recent NDA resubmission included a C-CASA analysis on suicide risk and tables of psychiatric adverse events. The sponsor concluded that “analyses of PSRAEs (possible suicide related adverse events) based on pooled data from 16 placebo-controlled, parallel-group studies in COPD patients and pooled data from 31 placebo-controlled studies in asthma, osteoarthritis, rheumatoid arthritis, and diabetes mellitus type 2 patients, do not suggest an association between roflumilast treatment and suicidality”.

DPARP Questions:

1. Please comment on the adequacy of the C-CASA assessment performed by the sponsor. Was the C-CASA properly executed? Do you agree with the sponsor’s conclusion that there was no association between roflumilast treatment and suicide?
2. Given that the C-CASA evaluation was performed adequately, do you feel there is an increased risk for suicidality in patients receiving roflumilast?
3. Does the increased risk (if any) of suicidality in patients receiving roflumilast justify a REMS that includes a Boxed Warning for suicide and increased psychiatric adverse events such as depression, anxiety and insomnia?
4. Do you have any additional comments regarding this NDA resubmission, including, but not limited to, the sponsor’s REMS, analysis on suicide, depression, anxiety, insomnia or other psychiatric adverse events?

Resubmission is in the EDR dated, August 30, 2010.

SIGNATURE OF REQUESTOR

Drs. Xuemeng Han Sarro and Tony Durmowicz (TL)

METHOD OF DELIVERY (Check one)

DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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CAROL F HILL  
10/13/2010



NDA 022522

**DISCIPLINE REVIEW LETTER**

Forest Research Institute, Inc  
Harborside Financial Center, Plaza V  
Jersey City, NJ 07311

Attention: Lisa L. Travis, M.S., RAC  
Director, Regulatory Affairs

Dear Ms. Travis:

Please refer to your July 15, 2009 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Daxas (roflumilast) Tablets, 500 mcg.

We also refer to your submission dated August 30, 2010.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have the following request for information.

1. Revise the test for purity (HPLC) method for the drug product to indicate that the reference and sample solutions are stable for (b) (4) as demonstrated in the validation report. The current wording in the method is inconsistent with these findings.
2. Revise the Content Determinations method (alternative b-HPLC) for the drug product to indicate that the reference and sample solutions are stable for (b) (4) as demonstrated in the validation report. The current wording in the method is inconsistent with these findings.
3. Provide confirmation that (b) (4) meets the USP monograph for (b) (4). Provide your specification for acceptance and a recent certificate of analysis.
4. The following preliminary comments pertain to the labels and labeling.
  - a. Revise the DESCRIPTION section to include the pharmacological or therapeutic class of the drug, as per 21 CFR 201.57(c)(12).
  - b. The prominence of the established name should be increased relative to the proprietary name, which is currently much more prominent due to the use of bold text.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

*{See appended electronic signature page}*

Prasad Peri, Ph.D.  
Acting Chief, Branch VIII  
Division of New Drug Quality Assessment  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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PRASAD PERI  
09/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE</b>		FROM: <b>Carol Hill, RPM. ODE II, DPARP/301-796-1226</b>		
DATE September 10, 2010	IND NO.	NDA NO <b>NDA 22522</b>	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT August 31, 2010
NAME OF DRUG <b>DAXAS (roflumilast) Tablets, 500mcg</b>		PRIORITY CONSIDERATION Standard – 6 month clock	CLASSIFICATION OF DRUG PDE4-inhibitor	DESIRED COMPLETION DATE January 7, 2011
NAME OF FIRM: Forest Research Institute, Inc.				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: <b>This is a class 2 resubmission of NDA 22522. The first cycle action was a complete response and labeling was not reviewed by the Division.</b> <a href="#">\\Cdsub1\evsprod\NDA022522\0029\m1\us</a> (August 30, 2010 – PI/Medication Guide) <a href="#">\\Cdsub1\evsprod\NDA022522\0000\m1\us\114-labeling</a> - (July 21, 2009 – carton and container) We are requesting a review of all submitted labeling.  Mid-Cycle Meeting: December 1, 2010 Labeling Meetings: December 13, 2010 Wrap-Up Meeting: January 4, 2011 PDUFA Date: February 28, 2010				
SIGNATURE OF REQUESTER Carol Hill		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22522

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ORIG-1

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FOREST  
RESEARCH  
INSTITUTE

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DAXAS(ROFLUMILAST 500  
MCG TABLETS

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/s/  
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CAROL F HILL

09/10/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>	
TO: <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) Carol Hill, RPM. ODE II, DPARP/301-796-1226	
REQUEST DATE September 10, 2010	IND NO.	NDA/BLA NO. <b>NDA 22522</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG DAXAS (roflumilast) Tablets 500 mcg	PRIORITY CONSIDERATION Standard – 6 month clock	CLASSIFICATION OF DRUG NME: PDE-4 Inhibitor	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) January 7, 2011
NAME OF FIRM: Forest Research Institute, Inc.		PDUFA Date: February 28, 2011	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION <input checked="" type="checkbox"/> NDA Resubmission	
<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION			
<b>EDR link to submission: This is a class 2 resubmission of NDA 22522. The first cycle action was a complete response and labeling was not reviewed by the Division. We request a review of all submitted labeling.</b> <a href="#">\\Cdsub1\evsprod\NDA022522\0029\m1\us (August 30, 2010 – PI/Medication Guide)</a> <a href="#">\\Cdsub1\evsprod\NDA022522\0000\m1\us\114-labeling - (July 21, 2009 – carton and container)</a>			
<b>Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.</b>			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  Mid-Cycle Meeting: December 1, 2010  Labeling Meetings: December 13, 2010  Wrap-Up Meeting: January 4, 2011			
SIGNATURE OF REQUESTER Carol Hill			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22522

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ORIG-1

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FOREST  
RESEARCH  
INSTITUTE

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DAXAS(ROFLUMILAST 500  
MCG TABLETS

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/s/  
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CAROL F HILL  
09/10/2010



NDA 22522

**ACKNOWLEDGE CLASS 2 RESPONSE**

Forest Research Institute, Inc.  
Plaza Five, Suite 1900  
Jersey City, NJ 07311

Attention: Lisa L. Travis, MS, RAC  
Director, Regulatory Affairs

Dear Ms. Travis:

We acknowledge receipt on August 31, 2010, of your August 30, 2010 resubmission to your new drug application for Daxas (roflumilast) Tablets, 500 mcg.

We consider this a complete, class 2 response to our May 17, 2010 action letter. Therefore, the user fee goal date is February 28, 2011.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
CPMS  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	FOREST RESEARCH INSTITUTE	DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

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CAROL F HILL  
09/10/2010

MIRANDA B RAGGIO  
09/10/2010

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 22522 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Daliresp Established/Proper Name: Roflumilast Dosage Form: Tablet		Applicant: Agent for Applicant (if applicable):
RPM: Carol Hill		Division: DPARP
<p><b>NDA:</b>                  NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)                  Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                  Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>February 28, 2011</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None   CR - May 17, 2010
❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> 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.

❖ Application Characteristics <sup>2</sup>	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request  Comments:  BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies  REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> 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.

<p>◆ Exclusivity</p>	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
<p>◆ Patent Information (NDAs only)</p>	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [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).

<p>(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?</p> <p>(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).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	February, 28, 2011 May 17, 2010
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**Officer/Employee List**

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP - February 28, 2011 CR - May 17, 2010
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**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	February 25, 2011
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	August 31, 2010 July 17, 2009
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/25/10  
Reference ID: 2914073

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	February 25, 2011
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	August 31, 2011 April 14, 2010
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	Acceptable - February 28, 2011 Non-Acceptable - December 20, 2011 Acceptable - July 23, 2010
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM December 17, 2010; May 10, 2010 <input checked="" type="checkbox"/> DMEPA May 5, 2010 <input checked="" type="checkbox"/> DRISK February 4, 2011 April 27, 2010 <input checked="" type="checkbox"/> DDMAC February 4, 2011; April 23, 2010 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	RPM Filing Review - May 10, 2010
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input checked="" type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>March 10, 2010</u>                If PeRC review not necessary, explain: <u>Indication is COPD</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> <li>Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)</li> </ul>	February 24, 18, 14, 11, and 2, January 21, 20, 12, and 10, 2011; December 6, October 14, September 21 and 10, August 31 and 17, May 11, April 23, 5, and 2; March 16 and 3; January 29, 19, 11, and 5, 2010; December 2, September 29 and 15; August 29 and 4, 2009
<ul style="list-style-type: none"> <li>Internal memoranda, telecons, etc.</li> </ul>	February 7, January 4, 2011 and August 7, 2009
<ul style="list-style-type: none"> <li>Minutes of Meetings               <ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date of mtg</i>)</li> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No mtg <input type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg April 16, 2008 <input type="checkbox"/> No mtg December 6, 2001
<ul style="list-style-type: none"> <li>Advisory Committee Meeting(s)               <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> <li>48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> No AC meeting April 7, 2010 April 7, 2010
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None February 28, 2011 May 17, 2010
<ul style="list-style-type: none"> <li>Division Director Summary Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None February 25, 2011 May 14, 2010
<ul style="list-style-type: none"> <li>Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None February 28, 2011 February 7, 2011 May 7, 2010
<ul style="list-style-type: none"> <li>PMR/PMC Development Templates (<i>indicate total number</i>)</li> </ul>	<input type="checkbox"/> None February 28, 2011
<b>Clinical Information<sup>5</sup></b>	
<ul style="list-style-type: none"> <li>Clinical Reviews               <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul> </li> </ul>	See CDTL Reviews March 24, 2010 September 25, 2010 <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Financial Disclosure reviews(s) or location/date if addressed in another review                OR                If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)</li> </ul>	Clinical Review /March 24, 2010, Page 16

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None IRTQT Review - March 5, 2010 Division of Psychiatry Products - November 16, 2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	REMS Docs - April 14, 2010 <input type="checkbox"/> None February 8, 2010 April 27, 2010
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested August 10 and 5, July 2, May 3, and April 23, 2010
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None January 14, 2011 March 31, 2010 September 29, 2009
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 4, 2011 April 26, 2010 April 23, 2010 March 23, 2010 September 26, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None October 4, 2010 April 23, 2010

<b>Nonclinical</b> <input type="checkbox"/> None	
<b>Pharmacology/Toxicology Discipline Reviews</b>	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None May 14, 2010
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None February 24, 2011 February 4, 2010 March 31, 2010
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None January 26 2011 March 19, 2010 September 26, 2009 Referenced IND 57883 Reviews: January 25, 25, 2010, June 6, 2007, Januray 1, 2003, May 29, 2001, July 24, 2000
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None January 25, 2010 Included in P/T review, page163
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
<b>Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 4, 2011 May 10, 2010
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 31, 2010
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 23, 2011 February 10, 2011 November 8, 2010 September 14, 2010 January 25, 2010 December 10, 2009 August 28, 2009
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> ) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	August 28, 2009
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: February 22, 2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> 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.

## 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.

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22522 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Daxas Established/Proper Name: Roflumilast Dosage Form: Tablet		Applicant: Forest Research Institute, Inc. Agent for Applicant (if applicable):
RPM: Carol Hill		Division: Division of Pulmonary, Allergy and Rheumatology Products
<p><u>NDA's:</u> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2) Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><b>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to <a href="#">CDER OND IO</a> for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</b></p> <p><b><u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.</b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>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.</b></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>May 17, 2010</u></li> </ul>		<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
<b>❖ If accelerated approval, were promotional materials received?</b> Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> 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.

❖ Application Characteristics <sup>2</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority          Chemical classification (new NDAs only): Type 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>Comments:</p>	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> 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	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [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).*

<p>(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?</p> <p>(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).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	April 28, 2010
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) CR - May 17, 2010
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	April 14, 2010
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	July 17, 2009
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	April 14, 2010
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	April 23, 2010
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	Acceptable - July 23, 2009 June 30, 2009
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM September 24, 2010 <input type="checkbox"/> DMEPA May 5, 2010 <input type="checkbox"/> DRISK April 27, 2010 <input type="checkbox"/> DDMAC April 23, 2010 <input type="checkbox"/> CSS NA <input type="checkbox"/> Other reviews NA
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	September 29, 2009
❖ 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input checked="" type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>March 10, 2010</u> If PeRC review not necessary, explain: <u>indication is COPD.</u></li> <li>• Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	May 11, 2010, April 23, 5, and 2, March 16 and 3, January 29, 19, 11, and 5, 2010, December 2, September 29 and 15, August 29 and 4, 2009

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 12/4/09

❖ Internal memoranda, telecons, etc.	August 7, 2009
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg April 16, 2008
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg December 6, 2001
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	April 7, 2010
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	April 7, 2010
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 17, 2010
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 14, 2010
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 7, 2010
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See CDTL Review
• Clinical review(s) ( <i>indicate date for each review</i> )	March 24, 2010 September 25, 2009
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical Review/March 24, 2010 page 16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None IRTQT Review/March 5, 2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	April 14, 2010 See Labeling/DRISK/April 27, 2010 <input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested May 3, 2010

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 12/4/09

<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 31, 2010 September 29, 2009
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 26, 2010 April 22, 2010 March 23, 2010 September 26, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None April 23, 2010
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 14, 2010
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 31, 2010
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 19, 2010 September 26, 2009 Referenced IND 57883 Reviews January 25, 2010, June 6, 2007, January 1, 2003, May 29, 2001, July 24, 2000
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None January 25, 2010 Included in P/T review, page163
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 10, 2010
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 31, 2010
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None January 25, 2010 December 10, 2009 August 28, 2009

❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> ) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	August 28, 2009
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> )	Date completed: August 27, 2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

## 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.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22522

-----  
ORIG-1

-----  
FOREST  
RESEARCH  
INSTITUTE

-----  
DAXAS(ROFLUMILAST 500  
MCG TABLETS

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

CAROL F HILL  
05/17/2010



NDA 22522

**DISCIPLINE REVIEW LETTER**

Forest Research Institute, Inc.  
Harborside Financial Center  
Plaza Five, Suite 1900  
Jersey City, NJ 07311

Attention: Lisa L. Travis, M.S., RAC  
Director, Regulatory Affairs

Dear Ms. Travis:

Please refer to your July 15, 2009 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Daxas (roflumilast) Tablet, 500 mcg.

In preparation for our April 7, 2010, Advisory Committee Meeting, we cancelled the labeling teleconference scheduled for April 6, 2010 with anticipation of rescheduling the teleconference for a future date. This letter is to notify you that we will not schedule a labeling teleconference during this review cycle. During the ongoing review of roflumilast for maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations, we have identified certain deficiencies and determined that the deficiencies preclude discussion of labeling at this time. Comments regarding these deficiencies are listed below:

1. A potential safety signal of suicidality was identified during review of your application: five patients treated with roflumilast either successfully committed suicide or made suicide attempts compared to no patients who received placebo.
2. The potential safety signals of suicidality, weight loss, and malignancy seen in your clinical program will need to be managed by appropriate safe use strategy.

3.

(b) (4)

We will schedule a teleconference with you this week to discuss the status of your application. If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 301-796-1226

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22522

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SANDRA L BARNES

05/11/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary, Allergy and  
Rheumatology Products**

**Memorandum of Facsimile Correspondence**

Date: April 22, 2010

To: Lisa Travis, M.S., RAC, Director of Regulatory Affairs

Company: Forest Research Institute, Inc

Email: lisa.travis@frx.com

Phone: 201-386-2031

From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary, Allergy and Rheumatology Products

Subject: re: NDA 22-522

# of Pages: 4

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Thank you. Please confirm receipt.  
**carol.hill@fda.hhs.gov**

## MEMORANDUM OF TELECONFERENCE

**APPLICATION:** NDA 22-522  
**SPONSOR:** Forest Research Institute, Inc.  
**DRUG NAME:** Daxas  
**DATE:** March 19, 2010

### **Forest Research Institute, Inc. Representatives:**

**Lisa L. Travis, M.S., RAC, Director, Regulatory Affairs**  
**June Bray, Vice President, Forest Regulatory**  
**Kevin McDonald, Associate Director**  
**Ulo Palm, VP Clinical, Respiratory**  
**Jonathan Jaffe, Exec Director, Clinical**  
**Paul Rowe, Associate Director, Clinical, Respiratory**  
**Andris Kalupnieks, Director, Pharmacovigilance**  
**Puneet Sachdev, Project Management**  
**Marco Tagliette, CMO**  
**Christoph Bunte, Nycomed Regulatory**  
**Susanne Heliland Kunath, Director, Nycomed Regulatory**

### **Division of Pulmonary, Allergy and Rheumatology Products Representatives:**

Badrul A. Chowdhury, M.D., Ph.D., Division Director  
Sally Seymour, M.D., Deputy Director of Safety  
Anthony Durmowicz, M.D., Clinical Team Leader  
Jayne Peterson, Supervisor, Advisors and Consultants Staff, Office of Executive Programs  
Kristine Khuc, Pharm.D., Advisors and Consultants Staff, Office of Executive Programs  
Carol Hill, M.S., Regulatory Health Project Manager

### **BACKGROUND:**

As a follow-up to the March 4, 2010 teleconference and after review of the Advisory Committee (AC) briefing document provided by Forest Research Institute, the Division scheduled a teleconference to address the issues that will be presented and discussed at the April 7, 2010 AC meeting.

### **Discussion:**

The Division stated that the purpose of the teleconference was to outline issues that will be addressed at the AC meeting. The Division commented that Forest's briefing document included a formal assessment of suicidality using the Columbia classification algorithm of suicide assessment (C-CASA) on a population of COPD patients and inquired if the NDA submission included any of the data from this assessment. Forest stated that the assessment was commissioned after the transfer of ownership of the application. Since the assessment was late in the review process, they decided to include the information in the briefing document. The Division noted that the presentation of the assessment in the briefing

materials implies that the information had been submitted to the NDA and was available for the Division to review. In addition, for these types of analysis the Agency usually participates in identifying the clinical trials and patient populations that will be assessed. Forest mentioned that these types of analyses have been employed by the Agency in the past, however; there was no intent to claim the Agency's agreement with the results.

Continuing from the previous conversation with Forest on March 4, 2010, regarding the format of the AC meeting, the Division reiterated that Forest's change in indication would be made known to the Advisory Committee and a discussion of the change was included in the Division's briefing document. Forest stated that it was understood that the change in indication would be presented and asked if the revised labeling would also be mentioned and/or discussed. Forest asked how the Division would present the information if it was decided to inform the committee about the submission of revised labeling. The Division responded that they would acknowledge Forest's intent to revise the label with the committee members. Forest mentioned that they would be amenable to discuss a Risk Evaluation and Mitigation Strategies (REMS) proposal with the Division if they felt it would be helpful. The Division stated that it would not be helpful to discuss a REMS that had not been formally submitted to the NDA, especially so close to the AC date.

The Division concluded by remarking their surprise of Forest's inclusion of the C-CASA assessment since it was not submitted to the NDA or been reviewed by the Division. The Division stated that its presentations will include a summary on COPD drug development and an overview of drugs used for COPD including the approved drug theophylline and another PDE4 inhibitor that was studied in clinical trials for COPD. Forest stated that the Division's plan was clear and very well understood.

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/s/  
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CAROL F HILL  
04/23/2010



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** April 15, 2010

<b>To:</b> Lisa Travis, MS, RAC Director, Regulatory Affairs	<b>From:</b> Carol Hill, MS Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Email Address:</b> lisa.travis@frx.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-386-2031	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 22522 – Clinical Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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Your submission dated July 15, 2009, to NDA 22-522, is currently under review. We have the following comments or request(s) for information:

1. Submit information on the regional distribution of cancers/malignancies found in patients with COPD (COPD safety data base). Categorize based on whether patients received roflumilast 500 mcg, roflumilast 250 mcg, or placebo and both by specific country and region (N. America, S. America, Asia, etc.).
2. Submit information on the number of COPD patients who had adverse events of weight loss reported who also had a cancer/malignancy. Construct a 4X4 matrix table for patients with cancer/malignancy where study treatment (roflumilast 500 mcg or placebo) is on one side and # of patients with adverse events of weight loss or no adverse events of weight loss on the other side (see below).

	# pts with Wt. Loss AE	# pts without Wt. Loss AE
Roflumilast 500 mcg		
Placebo		

Submit your response to this request by close of business, April 19, 2010. If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: Durmowicz/April 14, 2010  
Clearance History: chill/April 15, 2010  
                          Barnes/April 15, 2010  
Finalized: chill/April 15, 2010

Application  
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Submission  
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CAROL F HILL  
04/15/2010



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

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FACSIMILE TRANSMITTAL SHEET

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DATE: April 5, 2010

<b>To:</b> Lisa L. Travis, MS, RAC Director, Regulatory Affairs	<b>From:</b> Carol Hill, MS Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute, Inc.	Division of Pulmonary and Allergy Drug Products
<b>Email address:</b> lisa.travis@frx.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-386-2031	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 22522 – Statistical Information Request

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**Total no. of pages including cover:** 3

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Comments:

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Document to be mailed:                      YES                      xNO

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Your submission dated July 15 2009, to NDA 22-522, is currently under review. We have the following comments and requests for information.

We believe that the following, additional data regarding the occurrence of cancer/tumors in patients in the roflumilast program may be useful for discussion at the upcoming Advisory Committee meeting for roflumilast. Provide pooled analyses for the overall occurrence of cancers/tumors in COPD patients comparing roflumilast 500 mcg, 250 mcg, and placebo. Include a breakdown by type and include an analysis excluding skin cancer.

Submit your response to this request by close of business tomorrow, April 6, 2010. If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: chill/April 5, 2010

Clearance History: Barnes/April 5, 2010

Abugov/April 5, 2010

Buenconsejo/April 5, 2010

Finalized: chill/April 5, 2010

Application  
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CAROL F HILL

04/05/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Psychiatry Products**

FROM (Name, Office/Division, and Phone Number of Requestor): **Carol Hill (301-796-1226), Division of Pulmonary, Allergy, and Rheumatology Products**

DATE  
**March 26, 2010**

IND NO.  
**NA**

NDA NO.  
**22-522**

TYPE OF DOCUMENT  
**NA**

DATE OF DOCUMENT  
**NA**

NAME OF DRUG  
**roflumilast**

PRIORITY CONSIDERATION  
**S**

CLASSIFICATION OF DRUG  
**phosphodiesterase inhibitor**

DESIRED COMPLETION DATE  
**April 7, 2010**

NAME OF FIRM: **Forest Laboratories**

### REASON FOR REQUEST

#### I. GENERAL

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

#### II. BIOMETRICS

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

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG SAFETY

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

#### V. SCIENTIFIC INVESTIGATIONS

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

**COMMENTS / SPECIAL INSTRUCTIONS:** Roflumilast is a phosphodiesterase inhibitor under review as a treatment for chronic obstructive pulmonary disease (COPD). In the clinical trials there is an imbalance of psychiatric AEs [anxiety, depression, suicides, and suicide attempts, (e.g., 3 suicides and 2 suicide attempts in the drug group and none in the placebo groups)]. Unknown to us and not submitted to the NDA was an assessment for suicide performed at Comumbia Univ. using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). The sponsor recently included in their briefing book a brief one paragraph summary of the C-CASA assessment for an upcoming advisory committee meeting on April 7, 2010. The psychiatric AE issue will likely be discussed at the AC meeting and we thought having a person from DPP familiar with the C-CASA assessment at the AC meeting would be helpful to address any specific questions. If DPP can't attend the AC meeting then perhaps we could briefly discuss any thoughts your group has on the data/C-CASA assessment. As mentioned, the sponsor did not submit this information or analysis to the NDA but included a brief summary (the only information we have about it) on page 88 of the company's AC briefing document (attached). The actual data regarding the psychiatric AEs can be found on pages 99-102 of the attached roflumilast clinical briefing document.

SIGNATURE OF REQUESTOR Anthony Durmowicz, MD	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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ANGELA H ROBINSON

03/26/2010

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**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy  
Products**

**Memorandum of Facsimile Correspondence**

Date: March 16, 2010

To: Lisa L. Travis

Company: Forest Research Institute, Inc.

Email: [lisa.travis@frx.com](mailto:lisa.travis@frx.com)

Phone: 201-386-2031

From: Carol Hill, MS  
Senior Regulatory Management Officer  
Division of Pulmonary and Allergy Products

Subject: April 7, 2009 AC Agenda and Labeling Revisions re: NDA 22-522

# of Pages: 4

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**[carol.hill@fda.hhs.gov](mailto:carol.hill@fda.hhs.gov)**

## MEMORANDUM OF TELECONFERENCE

**APPLICATION:** NDA 22-522  
**SPONSOR:** Forest Research Institute, Inc.  
**DRUG NAME:** Daxas (roflumilast)  
**DATE:** February 26, 2010

### **Forest Research Institute, Inc. Representatives:**

June Bray, Vice President, Regulatory  
Kevin McDonald, Associate Director, Regulatory  
Lisa L. Travis, M.S., RAC, Director, Regulatory Affairs  
Ulo Palm, VP Clinical, Respiratory  
Jonathan Jaffe, Exec director, Clinical, Respiratory  
Paul Rowe, Associate Director, Clinical, Respiratory  
Andris Kalupnieks, Director, Pharmacovigilance  
Puneet Sachdev, Project Management  
Udo Michael-Goehrig, Nycomed Clinical  
Christoph Bunte, Nycomed Regulatory  
Marco Taglietti, M.D. Chief medical Officer

### **Division of Pulmonary & Allergy Products Representatives:**

Sally Seymour, M.D., Deputy Director for Safety  
Anthony Durmowicz, M.D., Clinical Team Leader  
Xuemeng Han Sarro, M.D., Clinical Reviewer  
Carol Hill, M.S., Regulatory Health Project Manager

### **Summary of the Discussion:**

The Agency informed Forest that the purpose of the teleconference was to provide information regarding the April 7, 2010 Advisory Committee agenda and to discuss the revised draft labeling dated, January 29, 2010. An overview of the draft AC agenda was described. Forest has 1 hour and 15 minutes of time for presentation of the application. An additional 15 minutes is scheduled for clarifying questions. The Agency presentation will follow a morning break. The open public hearing will occur at 1pm. Discussion of the questions follows the open public hearing. Forest asked if they can extend their presentation to approximately 90 minutes. The Agency commented that at this time 1 hr & 15 minute timeline was being allotted to maintain the schedule for the meeting. Forest noted that they may not be able to adhere to the timeline due to the significant amount of safety and efficacy data. The Agency requested that Forest try to keep to the allotted time.

The Agency addressed the January 29, 2010 submission that included significant changes to the label and noted the change of the indication from maintenance treatment of COPD to a narrower indication to reduce exacerbations of COPD. The Agency noted that the application will be reviewed on the basis of the indication included in the original submission, dated July 17, 2009 and the AC meeting will be based

on the original submission. Forest inquired if the revised indication will be discussed with the advisory committee and/or included in the FDA's presentation and also will other changes be mentioned. The Agency responded that the change in indication and new Warning of neuropsychiatric events will be discussed at the AC. The Agency noted that an information request may be forthcoming regarding the neuropsychiatric events. The Agency noted that the change in indication has been problematic for many reasons, including the fact that AC members are screened on the indication submitted. Forest stated that it was not their intent to complicate the process.

Forest inquired if the draft briefing materials will be provided as scheduled and also will the Agency provide Forest with a copy of their comments and questions to the AC committee. The Agency stated that at this time, the briefing materials will be provided as scheduled, however; sharing the questions is not a usual practice. Forest stated that their briefing book will be submitted within one week. They have prospective analyses of time to first and second exacerbations and have also analyzed time to third exacerbation. Forest asked if new analyses on the time to 3<sup>rd</sup> exacerbation could be included in the briefing package. The Agency did not object to inclusion of this information but questioned whether they wanted to spend much time on presenting a post hoc analysis on a secondary endpoint.

Forest confirmed that their presentation will be focusing on the pivotal trials 124 and 125. Toxicology data will not be presented unless it is included in the Agency's presentation. The Agency stated that their presentation will be predominately clinical data unless there is relevant clinical pharmacology or nonclinical information that may impact the risk benefit assessment. Typically, a brief summary of the nonclinical and clinical pharmacology issues are included in the briefing package.

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CAROL F HILL  
03/16/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy  
Products**

**Memorandum of Facsimile Correspondence**

Date: March 16, 2010

To: Lisa L. Travis

Company: Forest Research Institute, Inc.

Email: [lisa.travis@frx.com](mailto:lisa.travis@frx.com)

Phone: 201-386-2031

From: Carol Hill, MS  
Senior Regulatory Management Officer  
Division of Pulmonary and Allergy Products

Subject: ECAC Update    Re: NDA 22-522

# of Pages: 3

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[carol.hill@fda.hhs.gov](mailto:carol.hill@fda.hhs.gov)

## MEMORANDUM OF TELECONFERENCE

**APPLICATION:** NDA 22-522  
**SPONSOR:** Forest Research Institute, Inc.  
**DRUG NAME:** Daxas  
**DATE:** January 29, 2010

### **Forest Research Institute, Inc. Representatives:**

Terry Martin, Ph.D., D.V.M., Lead Toxicologist  
Jose Freire-Moar, Ph.D., Lead Pharmacologist  
Charles Lindamood, Ph.D., Department Head, Toxicology and Pharmacology  
Lisa L. Travis, M.S., RAC, Director, Regulatory Affairs

### **Division of Pulmonary & Allergy Products Representatives:**

Anthony Durmowicz, M.D., Clinical Team Leader  
Molly Shea, M.D., Supervisor, Pharmacology/Toxicology  
Marcie Wood, Ph.D., Reviewer, Pharmacology/Toxicology  
Carol Hill, M.S., Regulatory Health Project Manager

### **Discussion:**

The Division commented that the teleconference was scheduled to provide Forest with an update of the Executive Carcinogenicity Assessment Committee's (ECAC) May 10, 2005 evaluation of the two year hamster carcinogenicity study nasal tumor findings. Originally, the nasal tumors were considered rodent specific due to the rodent exclusively producing the ADCP N-Oxide metabolite responsible for the tumor formation. The committee observed that humans did not produce the compound, ADCP N-oxide. The Division stated the ECAC has revised its earlier conclusion in light of new clinical pharmacokinetic data showing that ADCP N-oxide is observed in human plasma and urine. The nasal tumor finding is no longer concluded to be a rodent-specific finding. Forest questioned if the new finding would require any follow-up on their part. The Division responded that the change in the ECAC's conclusion of the relevancy of the rodent nasal tumors prompted the Agency to provide the information to the sponsor as soon as it was available. The teleconference is strictly to convey the recent findings of the ECAC.

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CAROL F HILL  
03/16/2010



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** March 3, 2010

<b>To:</b> Lisa L. Travis, M.S., RAC Director, Regulatory Affairs	<b>From:</b> Carol Hill, M.S. Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute, Inc	Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 201-524-9711	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-386-2031	<b>Phone number:</b> 301-796-2300

**Subject:** **NDA 22522 - Clinical Information Request**

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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Your submission dated July 17, 2009, to NDA 22522, is currently under review. We have the following comments or request(s) for information:

1. Provide a summary of the psychiatric adverse event data for roflumilast. Submit adverse event data for the preferred terms in the psychiatric SOC for all placebo controlled trials conducted with roflumilast. Submit the psychiatric SOC data in separate tables for fatal adverse events (deaths), serious adverse events, and adverse events. Provide this information for each clinical program: COPD, asthma, and “other”. Include a brief description of what trials were and were not included in the summary tables.
2. Submit patient narratives for all reports related to suicide (e.g. suicide, suicide attempt, suicidal ideation).
3. Include a summary of information from nonclinical studies regarding the effects of roflumilast on the central nervous system.

Provide your response to our request by COB on March 8, 2010. If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.



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Submission  
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Product Name

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/s/  
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CAROL F HILL  
03/03/2010



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 29, 2010

<b>To:</b> Lisa L. Travis, MS, RAC Director, Regulatory Affairs	<b>From:</b> Carol Hill, MS Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute, Inc.	Division of Pulmonary and Allergy Drug Products
<b>Email address:</b> lisa.travis@frx.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-386-2031	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 22-522 - Compliance and Statistical Information Request

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**Total no. of pages including cover:** 14

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**Comments:** Please acknowledge receipt.

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**Document to be mailed:**                      YES                      xNO

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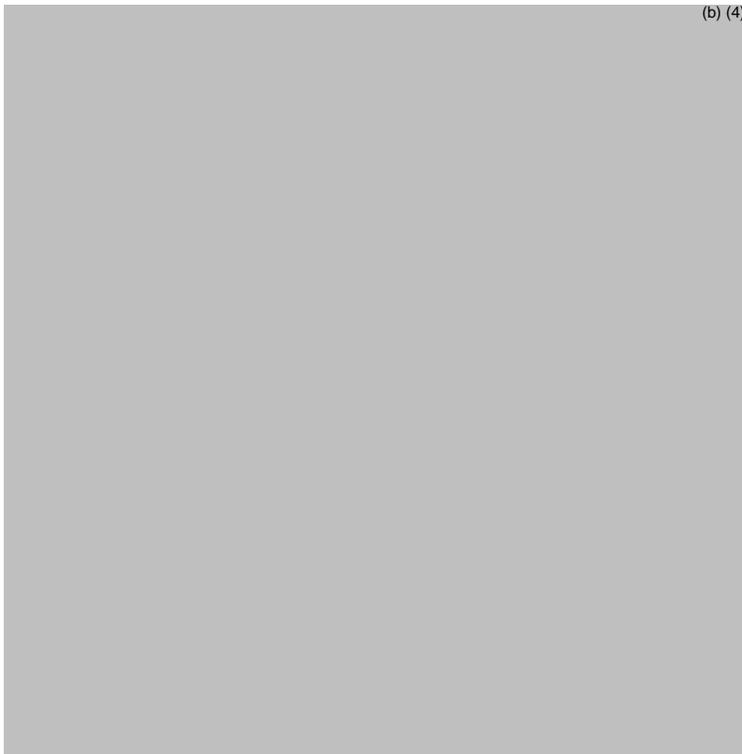
Your submission dated July 18, 2009, to NDA 22-522, is currently under review and we have the following compliance and statistical comments and/or requests for information. Submit your response to the compliance requests no later than February 5, 2010 and to the statistical requests no later than February 12, 2010.

## COMPLIANCE

- A. Provide the most current clinical site investigator contact information for the four clinical investigators identified in studies M2-124 and M2-125 such as, current complete street addresses, phone numbers, FAX numbers (if available), and e-mail addresses. Further, provide in PDF electronic format study subject data listings by clinical site and clinical investigator numbers for your well-controlled studies, M2-124 (Beatrix Balint, HUNGARY, Site #4545 and Neal Moser, KENTUCKY, Site #7176) and M2-125 (Anthony Mesquita, INDIA, Site 4793 and Halina Batura-Babryel, POLAND, Site #6675). The data listings should be unmodified and should be based on the NDA submission to the agency dated, e.g., "23.10.2008" for BY217/M2-125, and "7.10.2008" for BY217/M2-124. Provide this data in MM/DD/YYYY format, if possible. Otherwise, please specify the exact calendar date format. The study subject data listings should capture the following:
1. Subject randomization (if applicable per treatment group: site subject number, gender/age, randomization number, date of randomization if available). Please confirm that these were patients randomized, and add those that may have been missed (see the attachments).
  2. Subject discontinuation (if applicable per treatment group: site subject number, screening visit date, informed consent date, date of first dose/last dose, length of date of discontinuation, reason for discontinuation).
  3. Concomitant medications (non-study medications): (if applicable per treatment group: site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped).
  4. Prohibited medications (non-study medications): as above with concomitant medications
  5. Adverse events (if applicable per treatment group: MEDRA preferred term/investigator entry, detailed drug name, blinded-phase active dose, date start/stopped, severity/resolution)
  6. Serious adverse event/s (SAE) and death where applicable as in adverse event above, and dates of occurrence
  7. Protocol deviation/s: site subject number, date of occurrence, describe deviation e.g., informed consent obtained after baseline examination; serious adverse event not reported by site in a timely manner.

8. Primary efficacy endpoint (if applicable per treatment group: site subject number, visit number and corresponding date (screening, baseline, week 1...etc), pulmonary function test results (if three best were done, please provide all three)).
9. COPD exacerbations as part of the efficacy endpoint, including calendar dates, visit #, etc.

B. Provide contact information (phone numbers, FAX numbers, and e-mail address) and any updated contact personnel for the following:



## STATISTICAL

We received your proposal dated January 21, 2010, regarding how to respond to our Statistical Information Request. The proposal is acceptable.

We are also requesting that you provide the same sets of material for the following endpoints for all studies (FK1-101, M2-107, JP-706 and JP-708):

1. body weight for each visit,
2. patient Withdrawals, and
3. time to first and second exacerbation.

If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

9 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted: chill/January 28, 2010

Clearance: Barnes/January 28, 2010

Abugov/January 29, 2010

Buenconsejo/January 28, 2010

Orencia/January 28, 2010

Finalized: chill/January 29, 2010

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22522

-----  
ORIG-1

-----  
FOREST  
RESEARCH  
INSTITUTE

-----  
DAXAS(ROFLUMILAST 500  
MCG TABLETS

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/s/  
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CAROL F HILL  
01/29/2010

## REQUEST FOR CONSULTATION

TO (Office/Division):  
Division of Cardiovascular and Renal Products  
IRT QT Team

FROM (Name, Office/Division, and Phone Number of Requestor):  
Carol Hill, PM, x1226  
ODE II/Division of Pulmonary and Allergy Products

DATE  
January 12, 2010

IND NO.

NDA NO.  
22522

TYPE OF DOCUMENT  
Original NDA

DATE OF DOCUMENT  
July 15, 2009

NAME OF DRUG  
Daxas (roflumilast)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Phosphodiesterase type IV  
(PED4) inhibitor

DESIRED COMPLETION DATE  
February 26, 2010

NAME OF FIRM: Forest Research Institute, Inc.

### REASON FOR REQUEST

#### I. GENERAL

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

#### II. BIOMETRICS

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

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG SAFETY

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

#### V. SCIENTIFIC INVESTIGATIONS

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

**COMMENTS / SPECIAL INSTRUCTIONS:** This is a request for review of TQT Study Protocol No. CP-069. The submission is in the EDR, dated July 15, 2009. The PDUFA date is May 17, 2010. Associated IND 57883. Indication: COPD

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	NYCOMED GMBH	DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

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CAROL F HILL  
01/12/2010



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

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FACSIMILE TRANSMITTAL SHEET

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DATE: January 11, 2010

<b>To:</b> Lisa L. Travis, MS, RAC Director, Regulatory Affairs	<b>From:</b> Carol Hill, MS Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute, Inc.	Division of Pulmonary and Allergy Drug Products
<b>Email address:</b> lisa.travis@frx.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-386-2031	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 22522 – CMC Information Request

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**Total no. of pages including cover: 3**

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Your submission dated Jul 15 2009, to NDA 22-522, is currently under review. We have the following comments and requests for information.

1. The revised document with code SMP01E.25138DM, provided in response to comment 1 of our discipline review letter, specifically states that (b) (4) it marks the beginning of 1) the description of the manufacturing process in detail and 2) the manufacturing process in full compliance with GMP requirements.” This contradicts your response that indicated that this document was revised to indicate that “the manufacturing process from (b) (4), will be under GMP control.” Please revise all pertinent documentation in the application so that it is clear that the synthesis of Roflumilast is under full compliance with GMP requirements from the (b) (4) starting material.
2. Revise the HPLC method (SAS01E.001964QU) for determination of identity and purity of roflumilast to clarify that the system suitability resolution requirement (b) (4) applies to the closest eluting peaks (i.e., BYK20839 and BYK22868). This was not clear from the description in the method.
3. Current USP <621> CHROMATOGRAPHY does not state that a precision system suitability test is not required for purity tests. Regardless, the Agency recommends the inclusion of a precision requirement in impurities/degradation methods that use external or internal standards (see *Reviewer Guidance: Validation of Chromatographic Methods*, November 1994). Revise the HPLC methods (SAS01E.001964QU and SAS01E.001965QU) for determination of identity and purity of roflumilast to include precision requirements for multiple injections of the impurities at the limit of quantitation (b) (4)
4. Agree to revisit the drug substance particle size distribution (PSD) acceptance criteria after you have prepared multiple (e.g., n = 10) commercial batches that are used to produce drug product that meets the specification, and to weigh these against the data, making adjustments that will reflect the PSD data and take into consideration the variability in those data.
5. Revise the “End-of-shelf-life specifications” in sections 3.2.P.8.1.1.4 for the bottled, blister packaged, and bulk packaged drug product such that they reflect the updated specification dissolution requirement with  $Q = (b) (4)$  at 30 minutes.

Provide your response to this request no later than January 22, 2010. If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted by: chill/January 11, 2009  
Clearance History: Barnes/January 11, 2009  
Bertha/January 11, 2009  
Peri/January 11, 2009  
Finalized: chill/January 11, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22522	----- ORIG-1	----- NYCOMED GMBH	----- DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/  
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CAROL F HILL  
01/11/2010



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

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FACSIMILE TRANSMITTAL SHEET

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DATE: January 5, 2010

<b>To:</b> Lisa L. Travis, MS, RAC Director, Regulatory Affairs	<b>From:</b> Carol Hill, MS Regulatory Health Project Manager
<b>Company:</b> Forest Research Institute, Inc.	Division of Pulmonary and Allergy Drug Products
<b>Email address:</b> lisa.travis@frx.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 201-386-2031	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 22522 – Statistical Information Request

**Total no. of pages including cover:** 3

Comments:

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Document to be mailed:                    YES                    xNO

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Your submission dated Jul 15 2009, to NDA 22-522, is currently under review. We have the following comments and requests for information.

1. To facilitate comparisons with your proposed pivotal analyses, provide analyses of data from dose ranging studies FK1101, M2-107, JP 706, and JP 708 which are consistent with the primary and secondary efficacy and safety analyses for the primary and secondary efficacy and safety variables in your statistical analysis plan for study M2-124.
2. In the exacerbation analyses for these studies, be sure to define exacerbation endpoints consistent with those of M2-124: Severe = Hospitalization or Death, Moderate = oral or parenteral glucocorticosteroids.
3. For these studies, include documentation for your analyses (computer code, including formats and macros, log files documenting program and macro execution, analysis-results-metadata.pdf, metadata-computational-section.pds, define.xml).
4. For these studies, include all analysis datasets.
5. For these studies, include in each analysis dataset all treatment arms.
6. For study M2-124, tabulation dataset dm does not record approximately 25 subjects listed in the analysis dataset adxesum (e.g., subjects 81003, 81029, 83226, 83301). Explain this apparent discrepancy and, if appropriate, where armcd data can be found for these patients. Conversely dataset dm records subject 84375 but it is not included in dataset adxesum. Explain this apparent discrepancy.

Provide your response to this request no later than February 12, 2010. If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: chill/December 18, 2009  
Clearance History: Barnes/December 24, 2009  
                    Abugov/January 5, 2010  
                    Permutt/January 5, 2010  
Finalized: chill/January 5, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22522	----- ORIG-1	----- NYCOMED GMBH	----- DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/  
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CAROL F HILL  
01/05/2010



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy Products**

**Memorandum of Facsimile Correspondence**

Date: December 2, 2009

To: Kevin B. Johnson, PhD, MBA, Associate Director, Regulatory Affairs

Company: Nycomed

Email: kevin.johnson@ppdi.com

Phone: 919-456-4442

From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary and Allergy Products

Subject: Statistical Information Request re: NDA 22522

# of Pages: 3

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Thank you.  
**carol.hill@fda.hhs.gov**

Your submission dated July 15, 2009, NDA 22522, is currently under review. We have the following requests for information:

The study report for M2-118 lists ten exacerbations, the dataset - submitted has zero exacerbations. Provide an "xe" tabulation dataset for study M2-118 consistent with the study report or explain why the study report is incorrect.

For studies listed in Table T-2.7.3.1 of report 22/2009, submission Section 2.73 entitled 'Summary of Clinical Efficacy,' provide an "xe" or other dataset which distinguishes moderate exacerbations associated with oral or parenteral glucocorticosteroid therapy (as in M2-124 and M2-125) from other types of exacerbations.

Provide a complete set of tabulation datasets for studies JP-106 and JP-108."

Your response to our request should be received no later than December 21, 2009. If you have any questions, contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: chill/November 24, 2009

Clearance History: Barnes/November 25, 2009

Abugov/December 2, 2009

Li/December 2, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	NYCOMED GMBH	DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

CAROL F HILL  
12/02/2009



NDA 22522

**FILING COMMUNICATION**

Nycomed GmbH  
c/o PPD Development, LP  
1400 Perimeter Park Drive  
Morrisville, NC 27560

Attention: Kevin B. Johnson, Ph.D., MBA  
Associate Director, Regulatory Affairs

Dear Dr. Johnson:

Please refer to your new drug application (NDA) dated July 15, 2009, received July 17, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Daxas, (roflumilast) Tablet 500 mcg.

We also refer to your submissions dated August 24 and September 11, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is May 17, 2010.

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, mid-cycle, 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 April 6, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We do have the following request for information and preliminary labeling revisions.

1. Provide all macros and formats required to run submitted statistical programs for each of your phase 3 studies. For example, program t-exa-poisson.sas in study M2-124 will not

run without stratspecs.sas, which has not been included, requires calls to macros setup, setuplft, logscan, and countwords, which have not been included, and uses format sev, which has not been included."

2. Submit revised labeling incorporating the following revisions.

#### HIGHLIGHTS

- a. The Highlights must be limited in length to one-half page.
- b. If the drug is a member of an established pharmacologic class, the concise statement under the heading Indications and Usage must identify the class as follows: "(Drug) is a (name of class) indicated for (indications)".
- c. In the Adverse Reactions section, the manufacturer's name and phone number must be included in the verbatim statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**"

#### FULL PRESCRIBING INFORMATION: CONTENTS

- d. We recommend the use of a two-column format for the Table of Contents and that it be limited in length to one-half page

#### FULL PRESCRIBING INFORMATION

- e. After the Patient Counseling Information section at the end of the labeling include the manufacturer information

#### **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 full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22522	----- ORIG-1	----- NYCOMED GMBH	----- DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

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BADRUL A CHOWDHURY  
09/29/2009



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary and Allergy Products**

**Memorandum of Facsimile Correspondence**

Date: September 15, 2009

To: Kevin B. Johnson, PhD, MBA, Associate Director, US Regulatory Affairs

Company: PPD Development, LP

email: kevin.johnson@ppdi.com

Phone: 919-456-4442

From: Carol Hill, MS  
Regulatory Health Project Manager  
Division of Pulmonary and Allergy Products

Subject: Discipline Review Correspondence re: NDA 22522

# of Pages: 6

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Thank you.  
**carol.hill@fda.hhs.gov**

Please refer to your submission dated, July 15, 2009 to NDA 22522. Our preliminary review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Revise S.2.3 such that it is clear that the manufacturing process from the [REDACTED] (b) (4) forward, will be under GMP requirements. Specifically, the document entitled [REDACTED] (b) (4) [REDACTED] (document code SMP01E.25138DM) in S.2.3 is inconsistent with regard to this point.
2. Include an acceptance criterion for the purity of the [REDACTED] (b) (4) [REDACTED].
3. Revise the HPLC method (SAS01E.001964QU) for determination of identity and purity of roflumilast to include the specific system suitability tests, the acceptance criteria for this testing, and any changes that are to be made if the criteria are not met. System suitability parameters recommended include a capacity and tailing factor for the parent peak, resolution requirements for the closest eluting peaks (i.e., BYK20839 and BYK22868), and precision requirements for multiple injections of the impurities at the limit of quantitation.
4. Revise the HPLC methods (SAS01E.001964QU and SAS01E.1965QU) for determination of identity and purity of roflumilast to include sufficient detail in order to allow the analysts in Agency laboratories to verify these methods as suitable for regulatory purposes. For example, the current methods do not provide the detail for how samples and reference solutions are to be prepared, the injection sequence for the analyses, the system suitability criteria (see comments above below) that are applied, the maximum shelf lives of the various reference and sample solutions, the definitions of abbreviations, special instructions related to method robustness results, etc.
5. Revise the HPLC method (SAS01E.001965QU) for determination of identity and purity of roflumilast to include the specific system suitability tests, the acceptance criteria for this testing, and any changes that are to be made if the criteria are not met. System suitability parameters recommended include a capacity and tailing factor for the parent peak, resolution requirement between the parent peak and BYK204974, and precision requirements for multiple injections of the BYK204974 at the limit of quantitation.
6. Revise the title of method SAS01E.000828QU such that it is clear that it is for testing of residual solvent levels in the roflumilast drug substance, not the starting materials used to prepare roflumilast.
7. Revise the HPLC method (SAS01E.001963QU) for determination of content for roflumilast to include the specific system suitability tests, the acceptance criteria for this testing, and any changes that are to be made if the criteria are not met. System suitability parameters recommended include a capacity and tailing factor for the parent peak, resolution requirement between the parent peak and BYK20864, and precision requirements for multiple injections of the roflumilast.

8. Provide confirmation that the sulfated ash test for the drug substance is performed as per USP <281> not USP <733>. Revise the drug substance specification accordingly.
9. Provide confirmation that you will follow the recommendations of ICH Q7A, and place at least one batch of the roflumilast drug substance (unless none is produced that year) into the stability monitoring program and test at least annually to confirm the stability.
10. Provide data supporting the structural assignment of the drug substance related impurities  
(b) (4)
11. Based on the drug release for the various batches presented in fig. 3.2.P.2.1.1.1-1, interpolation, corresponding to drug product prepared with drug substance batches having median particle size at the upper limit of (b) (4) allowed by the particle size acceptance criteria, would lead to a predicted drug release of about (b) (4) at 30 minutes. Either provide data demonstrating that drug substance of the maximum particle size allowed by the acceptance criteria, produces drug product with acceptable dissolution or tighten the acceptance criteria for the particle size parameter of the drug substance specification. The current particle size acceptance criteria are very broad relative to the data observed for the May 2003 process validation and later batches.
12. Provide clarification, with drawings, of the in-process dimensions that are assessed for the tablet cores and film coated tablets.
13. Revise the drug product specification to include the specific acceptance criteria for each of the identity tests for roflumilast (e.g., "For identity check calculate relative retention time of roflumilast peak in test solution as quotient of retention time of peak in test solution and in reference injection solution. Identity is positive if quotient is in a range from (b) (4).").
14. Revise the drug product specification for dissolution such that  $Q = \frac{(b)}{(4)}$  at 30 minutes to assure 85% dissolution as outlined in Agency guidance for the setting of acceptance criteria for dissolution for immediate release dosage forms. Your stability data indicate that with  $Q = \frac{(b)}{(4)}$  at 30 minutes all tests would have passed at stage 1.
15. Provide confirmation that all of the potential degradants that can be quantified by the purity method used for testing of the drug product (b) (4) are soluble in the solvent used for the sample preparation. If this is not the case, the results obtained may not be an accurate quantification of the levels of these impurities actually in the intact dosage forms tested, as there is not complete dissolution during sample preparation.
16. Revise the method for testing the purity of the drug product to include system suitability acceptance criteria.
17. Revise the method for testing the identity and purity of the drug product to include the procedure for the roflumilast identity test similar to that given in 3.2.P.5.2.5.1.2.9 for the assay method.

18. Revise the method for testing the identity and purity of the drug product to clearly indicate that the column temperature must not exceed (b) (4), as indicated by the validation studies.
19. Revise the method for testing the identity and purity of the drug product to clearly indicate the maximum storage time and conditions for the prepared sample and reference solutions.
20. Revise the method for determination of the assay and content uniformity of the drug product (HPLC alternate b) to include system suitability acceptance criteria.
21. Revise the method for determination of the assay and content uniformity of the drug product (HPLC alternate b) to clearly indicate the maximum storage time and conditions for the prepared sample and reference solutions.
22. Revise the dissolution method for the drug product (for HPLC part) to include system suitability acceptance criteria.
23. Revise the dissolution method for the drug product (for HPLC part) to clearly indicate the maximum storage time and conditions for the prepared sample and reference solutions.
24. Provide assurance that you are confirming that the aluminum foil, from both suppliers, used for lidding for the blister packaging, is the correct temper (b) (4). This assurance is usually based on certificates of analysis (which were not provided in application) or based on appropriate physical testing upon your acceptance of this material.
25. It is not possible to confirm your conclusion that the bottled and blister packaged drug product are not susceptible to microbial contamination when you have not provided microbiological purity results from any time-points past the initial one in the stability studies. Modify the protocol and collect microbial purity data at the (b) (4) and report these to the Agency with your response. Conclusions regarding your proposed 24 month expiration dating periods are withheld pending the provision of these results.
26. Modify the post-approval commitment regarding the annual batches of drug product and the occurrence of out-of-specification (OOS) results. If OOS results are obtained from any of the annual batches, these should be withdrawn from the market. If you have evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, you should discuss this with the agency as soon as possible and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug or biological product must be reported under 21 CFR 314.81(b)(1)(ii) or 21 CFR 601.14, respectively.
27. Provide stability data for the drug product packaged in the bulk packaging outlined in P.7 to support the maximum length of time in use, and with the typical storage conditions during that time. (b) (4)

(b) (4) The package should meet the same requirements for protection, compatibility, and safety as a smaller market package. Alternatively, withdraw the repackaging site from the application.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Drafted: chill/September 11, 2009

Initialed: Barnes/September 11, 2009

Bertha/September 14, 2009

Peri/September 14, 2009

Al Hakim/September 14, 2009

Finalized: chill/September 15, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	NYCOMED GMBH	DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

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CAROL F HILL  
09/15/2009  
Signed for Sandy Barnes



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** August 29, 2009

<b>To:</b> Kevin B. Johnson, PhD, MBA Associate Dir., Reg. Affairs	<b>From:</b> Carol Hill, MS Regulatory Health Project Manager
<b>Company:</b> PPD Development LP On behalf of Nycomed	Division of Pulmonary and Allergy Drug Products
<b>email:</b> kevin.johnson@ppdi.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 919-456-4442	<b>Phone number:</b> 301-796-2300

**Subject:** NDA 22522 – Clinical Pharmacology Request for Information

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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, or a person authorized to deliver this document to 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 have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your submission dated 15 July 2009, NDA 22522, is currently under review. We have the following comments or request(s) for information:

Please submit all datasets for your population PK/PD report 175/2008 (especially the datasets for your exposure-safety analysis) and for your population PK report 252/2008 (Asthma patient population).

All datasets used for model development and validation should be submitted as SAS transport files (\*.xpt). Please add an additional column titled, SUBJECT in each of the datasets to represent the subject's unique ID that corresponds to the ID number in the safety and efficacy datasets.

A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt). A model development decision tree and/or table with an overview of modeling steps should be included.

If you have any questions, please contact Carol Hill, Regulatory Health Project Manager, at 301-796-1226.

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/s/  
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CAROL F HILL  
08/29/2009

## REQUEST FOR CONSULTATION

TO (Office/Division):  
**Division of Drug, Marketing, Advertising  
and Communications (DDMAC) WO 51 Wing 3200**

FROM (Name, Office/Division, and Phone Number of Requestor):  
Carol Hill, Project Manager, 301-796-1226  
Division of Pulmonary and Allergy Products

DATE 8/6/09	IND NO.	NDA NO. 22-522	TYPE OF DOCUMENT N	DATE OF DOCUMENT July 15, 2009
NAME OF DRUG Daxas (roflumilast)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG PDE4 inhibitor	DESIRED COMPLETION DATE March 12, 2009

NAME OF FIRM: Novartis Pharmaceuticals

### REASON FOR REQUEST

#### I. GENERAL

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

#### II. BIOMETRICS

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

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG SAFETY

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

#### V. SCIENTIFIC INVESTIGATIONS

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

**COMMENTS / SPECIAL INSTRUCTIONS:** This request is for review of the label of the new NDA submission. You may review the label, draft carton and container labels in the EDR submission dated, July 15, 2009.

Filing/Planning Meeting: August 25, 2009

Mid-Cycle Review: December 14, 2009

Labeling Meeting: February 15, 2009

Wrap Up: March 15, 2009

**PDUFA Date: May 17, 2010**

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

Wayne Amchin

PRINTED NAME AND SIGNATURE OF DELIVERER

Carol Hill

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22522	ORIG 1		DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

CAROL F HILL  
08/06/2009



NDA 22522

**NDA ACKNOWLEDGMENT**

Nycomed GMBH  
c/o PPD Development, LP  
7551 Metro Center Drive, Suite 300  
Austin, TX 78744

Attention: Dudley T. Womble, MPA, FACHE  
Manager, US Regulatory Affairs

Dear Mr. Womble:

We have received your new drug application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Daxas, (romflumilast) Tablet, 500 mcg

Date of Application: July 15, 2009

Date of Receipt: July 17, 2009

Our Reference Number: NDA 22522

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 September 15, 2009 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/oc/datacouncil/spl.html>. 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.

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 and Allergy 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/cder/ddms/binders.htm>.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Supervisory CPMS  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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CAROL F HILL

08/04/2009

Signed on behalf of Sandy Barnes

**MEMORANDUM**

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

**DATE:** August 7, 2009

**TO:** Kevin B. Johnson, PhD, MBA,  
Associate Director, Regulatory Affairs  
PPD Development, LP on behalf of Nycomed GmbH

**THROUGH :** Carol Hill, MS, Regulatory Health Project Manager

**FROM:** Prasad Peri, PhD, PAL, ONDQA, Branch 2 (CMC)

**SUBJECT:** Request for Site Fax Numbers

**APPLICATION/DRUG:** NDA 22522/Daxas (roflumilast)

Email sent on behalf of CMC to request fax numbers for the following sites:



Applicant was requested to forward the information by COB August 10, 2009 via fax and to submit the response formally to the application as a response to CMC information request.

---

Carol Hill, MS  
Regulatory Health Project Manager



Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22522	----- ORIG 1	-----	----- DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

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CAROL F HILL  
08/07/2009



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA for COPD  
**Meeting Date and Time:** April 16, 2008, at 3:00  
**Meeting Location:** White Oak Room 1311  
**Application Number:** IND 57,883  
**Product Name:** roflumilast  
**Received Briefing Package** March 7, 2008  
**Sponsor Name:** Nycomed  
**Meeting Requestor:** Cheryl Czachorowski  
**Meeting Chair:** Badrul Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Ladan Jafari  
**Meeting Attendees:**

**FDA Attendees:**

Banu Karimi-Shah, M.D., Medical Reviewer  
Sally Seymour, M.D., Medical Team Leader  
Luqi Pei, Ph.D., Preclinical Reviewer  
Timothy McGovern, Ph.D., Preclinical Supervisor  
Partha Roy, Ph.D., Clinical Pharmacology Reviewer  
Wei Qiu, Ph., D., Clinical Pharmacology Team Leader  
Feng Zhou, Ph.D., Biometrics Reviewer  
Qian Li, Ph.D., Biometrics Team Leader  
Badrul Chowdhury, M.D., Ph.D., Director  
Ladan Jafari, Regulatory Health Project Manager

**Sponsor Attendees:**

Manja Brose, Biometrician, Data Science  
Daniela Bundschuh, Ph.D. Project Management, Daxas  
Christoph Bunte, Ph.D., Senior Regulatory Affairs Manager  
Cheryl Czachorowski, Director, Regulatory Affairs US  
Udo-Michael Göhring, MD., Senior Medical Expert, Medical Scientific Strategy  
Susanne Heiland-Kunath, Ph.D., Head of Regulatory Development

Anke Heuser, Ph.D., Senior Research Scientist, Toxicological Pathology  
Andreas Hünemeyer, MD., Senior Research Scientist, Pharmacometrics  
Vimala Rahm, MD., Senior Medical Expert, Corporate Drug Safety  
Christian Wrehlke, Ph.D., Regulatory Submission Manager  
Volkmar Zingel, Ph.D., Head of CMC Management  
Ulrich Freudensprung, Biometrician, Data Science

**Background:** Nycomed submitted a Pre-NDA meeting request dated January 28, 2008, to discuss the submission of an NDA for roflumilast for COPD. Nycomed also submitted a briefing package dated March 6, 2008, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to Nycomed's questions via FAX on April 14, 2008. The content of that FAX is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Nycomed's questions are in bold italics; FDA's response is in Italics; discussion is in normal font.

**CMC:**

**Starting Materials for Synthesis**

- 1. The objective of the chemical development program was to establish a robust chemical process for the drug substance roflumilast. The starting materials for the synthesis were chosen based upon the principles as described in the ICH Guidance Topic Q7 A, "Good Manufacturing practice for Active Pharmaceutical Ingredients". The sponsor believes that*** (b) (4)

(b) (4)

*satisfy the criteria for designation as starting materials in the GMP synthesis of roflumilast. Section 5 of the Briefing Package contains information to support this position. This section summarizes the extensive development and characterization work needed for the accurate selection of the starting materials* (b) (4) *It covers all aspects like synthesis, potential impacts of side reactions, impurities, analyses and quality requirements.*

***Does the Agency agree that the*** (b) (4) ***may be designated as the starting materials in the synthesis of roflumilast?***

**Response:**

*While your characterization for the impurities and side products for the* (b) (4) *seem reasonable, we need assurance that the synthetic route and manufacturing processes for the* (b) (4) *remain well controlled at all times (pre-approval and post approval).*

*Given the fact that you have not provided any assurance on the consistency of the synthetic route once the* (b) (4) *is designated as starting material and the fact that the* (b) (4) *is not commercially available, we do not agree to designating the* (b) (4) *as a starting material. We recommend that you provide complete CMC information for the* (b) (4) *in the NDA or appropriately authorized drug master file (DMF).*

We concur with naming the (b) (4) as a starting material.

The proposed acceptance criteria for the (b) (4) will be a review issues in the NDA.

### **Stability Program**

- 2. Nycomed has lately developed a tablet (b) (4), as the dosage form proposed for future commercialization. This dosage form**

(b) (4)

(b) (4)

*Two different container closure systems, i.e. bottles and blisters, have been integrated in the studies. Both container closure systems are intended for distribution, either for commercialization (bottles) or to be provided as samples (blisters).*

*Primary stability information on full-scale drug product, i.e. 500 mcg roflumilast film coated tablet (Formula E) batches packed in 60 cc high density polyethylene (HDPE) bottles and (b) (4) blister material have been stored since March/April 2007.*

*In addition, further three batches of Formula E, each packed in two different (b) (4) blister, have been placed on stability beginning October 2007.*

*Dependant on the outcome of the stability studies using different primary packaging materials, Nycomed will propose a suitable container closure system for the market. Depending on the selected packaging material for commercialization and depending on the start of the stability studies with the different packaging materials, at least twelve (12) to eighteen (18) months of stability data from these studies will be included in the initial NDA filing in March 2009. Eighteen (18) months data to twenty-four (24) months data will be available in June 2009 and 3 months after the planned NDA submission date to update the NDA and to support the stability in the proposed commercial packaging materials. Pending satisfactory data along with thorough data analysis a shelf-life of either 24 (b) (4) months will be proposed.*

- a. ***Does the Agency agree that the stability program is sufficient to support the shelf life of the drug product?***
- b. ***Does the Agency concur with Nycomed's proposal to update the NDA, during review, with recent stability data without affecting the review clock?***

**Response:**

*Your proposed stability program seems to be lacking the intermediate storage condition (30°C/65 % RH conditions). We remind you that you are taking a risk with this approach.*

*The shelf life of the drug product will depend on the real time stability data available in the initial NDA. While you may submit updated stability data to the NDA during the review cycle, note that there is no assurance that the updated data will be reviewed within the review cycle. You may potentially get a shelf life based on the data in the initial NDA.*

**Batch Records**

3. ***To meet the requirements of 21 CFR 314.50 (d) (1) (ii) (b) and 21 CFR 314.50 (d) (1) (ii) (c), in section 3.2.R of the NDA, the sponsor proposes to provide a copy of an executed batch record (German/English) from one of the ICH primary stability batches, i.e. 500 mcg roflumilast film-coated tablet (Formula E). This batch was also***

(b) (4)

*In addition, the sponsor will provide a copy of an executed batch record (German/English) of the 500 mcg roflumilast uncoated tablet batch (Formula B) used* (b) (4) *as well as an executed batch record (German/English) of a representative tablet batch (Formula B) which was applied in the pivotal clinical trials (BY217/M2-124 and BY217/M2-125).*

*A copy of the executed batch record (German/English) of the* (b) (4)

*will also be included. This study was performed to support the site change from the* (b) (4) *to the proposed production site.*

*In addition, we will provide an English translation of the proposed master batch record intended to be used to manufacture the marketed product. Associated documents (e.g., excipient certificates of analysis) will be available upon request, as will the executed batch records for the remaining two ICH stability batches and for the remaining batches used in bioequivalence studies.*

**Does FDA agree with the proposed submission plan for drug product batch records?**

**Response:**

*Your proposal is acceptable.*

**Additional CMC Comments**

- a) *Include a well documented Pharmaceutical Development Report as per ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.*
- b) *At the beginning of the CMC section, include a table of all facilities (including contract manufacturers/testers etc. for drug substance and drug product), include specifically what is the function of each facility, the contact name and address, the CFN number, and the complete name and address of the facility.*
- c) *Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.*
- d) *Provide tabular summaries of your stability data, organized by test parameter, and separated by manufacturing site, batch, storage condition and container closure system. Provide graphical summaries of any trending stability data, organized by test parameter, including mean and individual data.*
- e) *We refer you to the guidance documents for impurities in the drug substance (ICH Q3A) and drug products (ICH Q3B(R2)) available at the FDA website. Special considerations should be given to impurities deemed as structural alerts (potential for genotoxicity).*
- f) *Provide a table referencing the drug product formulation used in all clinical trials, in the NDA submission*
- g) *We refer you to our previous CMC comments provided in the Agency's letter dated June 29, 2007. Address them adequately in the NDA.*

**Nonclinical:**

4. *Section 6 of the Briefing Package includes an overview on pharmacology, pharmacokinetics and toxicology studies performed with roflumilast. Section 3 provides the draft table of contents for the NDA including information on how Module 4 will be organized.*

***a. Is the Agency in agreement that the studies included in Module 4 constitute a complete nonclinical package for filing the roflumilast tablets NDA and that enough information is included that will allow FDA to make a decision on the approval of roflumilast tablets?***

**FDA response:**

*Yes, we agree that your nonclinical data constitute a complete package for a NDA submission. The adequacy of the nonclinical data in support of approval of the drug will be a review issue.*

***b. Is the Agency in agreement with how the studies are organized in Module 4 as described in the draft table of contents located in Section 3 of the Briefing Package?***

**FDA response:**

*Yes, we agree with your organization of the nonclinical data.*

#### **Carcinogenicity Datasets**

***5. Datasets for the three carcinogenicity studies with roflumilast (Report No. 97/2001 (mouse); Report No. 7/2002 (hamster); Report No. 233/2003 (hamster)) have been submitted to the Division in IND Serial No. 0265 dated February 18, 2004. The Executive Carcinogenicity Assessment Committee (ECAC) reviewed the carcinogenicity data and concluded at its meeting on May 10, 2005 that***

***“the mouse study was adequate and negative for drug-induced tumors” and that “the hamster studies were adequate and the nasal-neoplasms in the two hamster studies may be due to a rodent-specific metabolite and thus may not be relevant to humans.”***

***Since then, no further information was gained that would change this evaluation. Therefore, the sponsor considers the conclusion on the roflumilast carcinogenicity studies as final.***

***Does the Agency agree that no datasets for the three carcinogenicity studies have to be submitted with the NDA since these data have already been submitted and assessed by the CAC?***

**FDA response:**

*Yes, we agree that you do not need to submit the datasets for the 3 animal carcinogenicity studies. Resubmit reports of these studies.*

**Discussion:**

- Nycomed indicated that based on the response to Question 4 and 5, they understood that no datasets containing nonclinical data were required for submission with the original NDA submission. Nycomed requested the Division to confirm that their understanding is correct.
  - The Division stated that it is not a requirement to submit the electronic datasets for nonclinical studies other than the carcinogenicity studies and noted that Nycomed has already submitted them. It is, however, helpful to submit the electronic datasets for chronic toxicity studies and pivotal reproductive toxicity studies if it does not cause extra burden. The Division reiterated that all nonclinical study reports must be submitted with the NDA.

**Clinical:**

**Module 5 - Overall Content and Organization:**

6. *The clinical development program for roflumilast for the treatment of COPD is described in detail in Section 7 of the Briefing Package. Clinical study reports are organized in Module 5 in accordance with recommendations set forth in CTD Guidance and are presented in the draft table of contents provided in Section 3 of the Briefing Package.*
  - a. *Is the Agency in agreement with how the studies are organized in Module 5 as described in the draft table of contents located in Section 3 of the Briefing Package?*

**Response:**

*We agree.*

- b. *Does the Agency concur that the proposed clinical package identified for inclusion in Module 5 will constitute a complete clinical package for filing the roflumilast tablets NDA and that enough information is included to allow FDA to make a decision on whether roflumilast is safe and effective for the proposed indication?*

**Response:**

*The proposed clinical package format identified in Module 5 appears appropriate for filing. The adequacy of the submitted data to support approval will be a review issue.*

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**8. Safety Datasets of Clinical Pharmacology Studies and Pharmacokinetic and Population Pharmacokinetic Datasets**

**Safety Datasets**

*In addition to datasets for Efficacy and Safety studies (see question 19), the sponsor intends to submit safety datasets of Clinical Pharmacology studies only for those studies that fulfill the criteria as follows:*

*Oral application of more than 500 mcg roflumilast QD*

*Special populations, i.e. pediatric population, liver and renal impaired subjects*

*Dedicated safety studies in healthy subjects, i.e. BY217/CP-069 (effects of roflumilast on cardiac repolarization, pharmacokinetics, safety, and tolerability in healthy volunteers).*

**Pharmacokinetic Datasets**

*The sponsor intends to submit pharmacokinetic (PK) datasets of Clinical Pharmacology studies (as summarized in sections 2.7.1 and 2.7.2 of the CTD) for roflumilast and roflumilast-N-oxide only for those studies that fulfill the criteria as follows:*

*Complete time-concentration profiles are available (i.e., PK datasets of studies providing only trough or sparse samples will not be submitted).*

*If similar PK information can be obtained from more than one study, only the more relevant and comprehensive datasets will be provided (e.g., datasets of study BY217/CP-050 (PK of 500 mcg roflumilast [15 days] in healthy elderly compared with healthy young and middle-aged subjects) will be submitted but not from study BY217/FHP024 (PK and safety of a single oral dose of 500 mcg roflumilast in healthy middle aged subjects (>45 and < 65 years)).*

**Population Pharmacokinetic Datasets**

*For population pharmacokinetic (pop-PK) analysis, the sponsor intends to submit index and validation PK datasets of selected clinical pharmacology and Phase III studies together with information on dose, age, sex, weight, smoking status, alcohol intake, food (fasted, fed) and race (Black, Caucasian, Asian and others).*

*For further details, especially for the rationale why datasets are not intended to be part of the NDA submission, please refer to Appendix 3 of the Briefing Package.*

*Does the Agency agree with the proposed approach?*

**Response:**

*For study BY217/CP-069, we request that you submit the following:*

- *Electronic data sets as SAS transport files*
- *SAS code for the primary statistical analysis*
- *Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis*
- *ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))*
- *A Define file which describes the contents of the electronic data sets*
- *If possible, submit all data sets in CDISC SDTM format*

*Otherwise, we agree to your approach of submitting safety, PK as well as Population PK datasets.*

**9. Clinical Efficacy - Format and Presentation of Data**

*The sponsor plans to present the efficacy data in an Integrated Summary of Effectiveness (ISE; see outline of text portion of ISE in Appendix 4 of the Briefing Package) in accordance with the “Guideline for the format and content of the clinical and statistical sections of an application” dated July 1988. The ISE including tables, figures, and datasets will be located in section 5.3.5.3 of Module 5. In accordance with the draft Guidance for Industry “Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document”, June 2007, the text portion of the ISE will also be located in section 2.7.3 (Summary of Clinical Efficacy) of Module 2.*

*Does the Agency agree with the proposed approach?*

**Response:**

*We agree.*

## 10. Content of the ISE

*The proposed ISE (see Appendix 4 of the Briefing Package) for the roflumilast tablet NDA besides describing individual results of important efficacy studies, will include study-to-study comparisons and integrated analyses. The 1-year studies BY217/M2-124 and BY217/M2-125 are conducted to investigate reduction in exacerbation frequency in severe COPD patients (post-FEV<sub>1</sub> of ≤50% predicted) with chronic bronchitis. These two studies are considered the pivotal studies for the targeted indication “maintenance treatment of patients with severe COPD associated with chronic bronchitis for the reduction of COPD exacerbations”.*

*Consequently, presentation in the ISE will focus on the results of the two pivotal studies, and their integrated analyses (pivotal COPD studies pool). The analysis across the two pivotal studies will focus on*

- *the primary efficacy variables (rate of exacerbations and pre-bronchodilator FEV<sub>1</sub>),*
- *the key secondary parameters post-bronchodilator FEV<sub>1</sub>, TDI Focal score, C-reactive protein, and all-cause mortality,*
- *the secondary parameters time to onset of exacerbations, severity of exacerbations and duration of exacerbations.*

*Results of further COPD studies (Studies BY217/FK1 101, BY217/FK1 103, BY217/M2-107, -110, -111, -112, -121, -127, -128) conducted in different patient populations and with different endpoints will be presented as supportive data.*

*Supportive data will include*

- *comparison of individual study results,*
- *an integrated analysis of 1-year studies having evaluated exacerbations as primary endpoint (M2-111+M2-112 pool with studies BY217/M2-111 and -112), and*
- *an integrated analyses of all studies of 6 months duration with lung function as primary endpoint (6-month studies pool with studies BY217/FK1 101, BY217/FK1 103, BY217/M2-107, -110, -121, -127, -128). Since the sponsor will apply only for one dose (500 mcg roflumilast), this integrated analysis will include only the comparison of Placebo and 500 mcg.*

*Efficacy variables for supportive data will include*

- *pre-FEV<sub>1</sub> for all studies and both integrated analyses,*
- *exacerbation rate for the individual Studies BY217/M2-111 and -112 and the integrated analyses of both studies.*

*Subgroup analyses will be performed for the three integrated analyses (Studies BY217/M2-124 and -125; studies BY217/M2-111 and -112; Studies BY217/FK1 101, BY217/FK1 103, BY217/M2-107, -110, -121, -127, and -128) as follows.*

*Major demographic factors (age, gender, race), geographic region (North-America (US + Canada), Europe, Rest of World) and other intrinsic and extrinsic factors (smoking status, disease severity, selected concomitant medication) will be evaluated. Subgroup analyses will focus on exacerbation rate and pre-FEV<sub>1</sub> as efficacy variables. Subgroup analyses for individual studies will be available in the clinical study reports.*

*In individual study reports different methodologies were used to analyze efficacy. Although only slight methods-related differences are expected between studies, most data will be reanalyzed using the methodology specified for the pivotal studies and the reanalyzed data will be presented and compared in section 3 of the ISE. The results as reported in the individual study reports will be presented in section 2 (Summary of results of individual studies) and in section 4 (Analysis of clinical information relevant to dosing recommendations) and in respective summary tables, which will be included in the Appendix of the ISE.*

*Studies omitted from the pooled data were of shorter duration (Studies BY217/IN-108, BY217/M2-119, -118, BY217/FHP 030), dissimilar in study design (Studies BY217/FK1 102 and BY217/FHP030, open-label or cross-over versus randomized placebo controlled) or were conducted under direction of a different sponsor in Japan (JP-706, JP-708). However, the results of these studies will be briefly described and summarized within the ISE (section 2).*

*For further details, see outline of the proposed ISE in Appendix 4 of the Briefing Package.*

- a. *Does the Agency agree that the overall proposed approach for the ISE (see Appendix 4 of the Briefing Package) is adequate for review and for decision on approval of the roflumilast tablet NDA?*

**Response:**

*The overall proposed approach for the ISE appears reasonable. The adequacy and completeness of the information within the ISE will be a review issue.*

*Your ISE should include a discussion of the important secondary endpoints, including FEV<sub>1</sub>, exacerbations, and mortality for your pooled one year studies and other supportive studies. Your product label may include negative findings from your clinical trials, not just the endpoints that were successfully achieved.*

**Discussion:**

- Nycomed requested further clarification on the FDA comment regarding "...and other supportive studies." Nycomed stated their intent is to analyze exacerbations (rate, duration, time to onset and severity) and mortality for the 1-year trials and the pooled 1 year trials. In their opinion an appropriate assessment of exacerbations should be based on trials of at least 1-year duration, which is also supported by the draft FDA guidance on COPD. Additionally, since mortality was not a formal endpoint in the 6-month trials, they do not intend to provide an analysis or discussion of exacerbation and mortality for the 6-month studies pool.

- The Division accepted Nycomed's proposal and indicated that the intent of our response was to convey that we will be looking at the totality of the data, and not just a statistically significant difference in the primary endpoint. The Division further stated that we would examine all endpoints and recommended Nycomed include a discussion in the ISE of the important secondary endpoints.

- b. *Does the Agency agree that the specified approach for pooling data is adequate?*

**Response:**

*We agree. However, we also request that you pool the results for the 4 one year clinical trials.*

- c. *Does the Agency agree that the specified approach for subgroup analyses is adequate?*

**Response:**

*We agree. The subgroup analysis should also be performed on the 4 pooled one-year clinical trials.*

**11. Clinical Safety - Format and Presentation of Data**

*The sponsor plans to present the safety data in an Integrated Summary of Safety (ISS; see outline of text portion of ISS in Appendix 6 of the Briefing Package) in accordance with the "Guideline for the format and content of the clinical and statistical sections of an application" dated July 1988. The ISS including tables, figures, and datasets will be located in section 5.3.5.3 of Module 5. In accordance with the draft Guidance for Industry "Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document", June 2007, a Summary of Clinical Safety will be extracted from the text portion of the ISS and located in section 2.7.4 of Module 2.*

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*Does the Agency agree with the proposed approach?*

**Response:**

*We agree.*

12. **ISS - Pooling of Data**

*The proposed Integrated Summary of Safety (ISS; see Appendix 6 of the Briefing Package) of the roflumilast tablet NDA includes safety data from all clinical studies (Phase I to III) of the clinical development program for roflumilast tablets. Reference to preclinical studies will be included as needed, such as, in case special safety studies were performed on a safety issue observed in preclinical studies, e.g. toxicity of roflumilast on reproduction in rats (study RR0414) and effects of roflumilast on male reproductive parameters in healthy subjects (study BY/217/FHP035).*

*The proposed ISS will describe safety data from individual studies in a table format and integrated analyses. The integrated safety data from the two pivotal COPD studies, BY217/M2-124 and -125, will serve as the primary basis for developing the roflumilast safety profile. Additional COPD studies, (Studies BY217/FK1 101, BY217/FK1 103, BY217/M2-107, -110, -111, -112, -118, -119, -121, -127, -128, BY217/IN-108), will be pooled with the pivotal studies and presented as supportive data and serve to corroborate the safety data from the pivotal studies. Signal analysis will be developed through the review of the safety data from the pivotal studies, the further COPD studies, additional pooled data as described in Table 2.1, and individual studies. Studies omitted from the pooled data (COPD + asthma) were dissimilar in study design (Studies BY217/FK1 102 and BY217/FHP030, open-label or cross-over versus randomized placebo controlled), or were conducted under direction of a different sponsor in Japan (JP-705, JP-706, JP-707, JP-708). Furthermore, the withdrawal arm (500 mcg roflumilast / placebo) of study BY217/FK1 103 will not be included in the pooled analyses. However, the results of these studies will be briefly described and summarized within the ISS (section 6).*

**Table 2.1: Summary of studies pooled for safety analyses**

<b><i>Safety Pool</i></b>	<b><i>Patient population</i></b>	<b><i>Studies</i></b>	<b><i>Patient numbers</i></b>
<b><i>Pivotal COPD studies pool</i></b>	<b><i>COPD</i></b>	<b><i>Pivotal COPD studies BY217/M2-124 and -125</i></b>	<b><i>3000 (estimated)</i></b>
<b><i>COPD safety pool</i></b>	<b><i>COPD</i></b>	<b><i>Pooled COPD studies BY217/FK1-101, -103 (without withdrawal arm), BY217/M2-107, -110, -111, -112, -118, -119, -121, -124, -125, -127, -128, BY217/IN- 108</i></b>	<b><i>11900 (estimated)</i></b>
<b><i>Asthma safety pool</i></b>	<b><i>Asthma</i></b>	<b><i>Placebo-controlled asthma studies: BY217/FK1-003, - 004, -011, -020, -021, BY217/FHP-031, BY217/M2-012, -013, -014, -023</i></b>	<b><i>5172</i></b>

***For the groups of***

- ***COPD studies omitted from pooled analyses***
- ***Non placebo-controlled, open label or cross-over asthma studies  
(comparator studies)***
- ***All phase I & healthy volunteers studies***
- ***Other indication studies (rheumatoid arthritis, osteoarthritis, diabetes,  
allergic rhinitis)***  
***no pooled analysis but a narrative integrated discussion of the individual studies will be  
provided.***

*Subgroup analyses will be performed for the pivotal COPD studies (pivotal COPD studies pool, see Table 2.1) and the pooled COPD studies (COPD safety pool, see Table 2.1). The subgroup analysis will be performed for the following intrinsic and extrinsic factors:*

*1) Gender: male/ female*

*2) Age: ≤65/ >65*

*3) Race: Caucasian/ Black/ Asian/ Other*

*4) Disease severity (post bronchodilator FEV<sub>1</sub>):*

*Pivotal COPD studies pool: <30% predicted, ≥30% predicted*

*COPD safety pool: <30% predicted, 30-50% predicted and ≥50% predicted*

*5) Geographic region: North-America (US and Canada)/ Europe / rest of world*

*6) Smoking habit: smokers/ ex-smokers*

- a. *Does the Agency agree that the overall proposed approach for the ISS (see Appendix 6 of the Briefing Package) is adequate for review and for decision on approval of the roflumilast tablet NDA?*

**Response:**

*In general, your approach for the ISS appears reasonable. See our response to part (b).*

- b. *Does the Agency agree that the specified approach for pooling data is adequate?*

**Response:**

*We acknowledge your approach for pooling the data. In addition, you should also provide an analysis of the studies pooled on the basis of trial duration. For example, pool all the one year studies, pool all the 6 months studies, and pool the shorter duration studies.*

**Discussion:**

- Nycomed proposed to conduct pooled analysis for three study durations: one year COPD studies, 6-month COPD studies, and 3-month COPD studies. They did not propose to provide pooled analysis by duration for asthma studies.

➤ The Division accepted Nycomed's proposal.

- c. *Does the Agency agree that the specified approach for subgroup analyses in the two COPD pools is adequate?*

**Response:**

*The subgroup analysis should be performed on the data pooled by study duration as well as the two COPD pools you have specified.*

**13. ISS - Topics of Interest**

*Analysis of certain safety topics of interest in the ISS will include those listed below.*

*Safety topics of interest based on roflumilast data include:*

*Identified safety topics:*

- *Weight decrease*

*Safety topics under review:*

- *Infections (TNF-alpha inhibition)*
- *Tumors (TNF-alpha inhibition)*

*Safety topics based on the development of other PDE4 inhibitors:*

*Safety topics under review:*

- *Mesenteric Vasculitis*
- *Cardiac Safety*

*Each topic of interest will include a section in the ISS that describes the identification of the events analyzed and the criteria used to determine an assessment of relevance to the roflumilast safety profile.*

*Does the Agency agree with the identified safety topics of interest?*

**Response:**

*We agree.*

**14. ISS – Clinical Laboratory Evaluations**

*In the proposed ISS, Clinical Laboratory Evaluations for the pooled data (section 3 of ISS) will be presented as shift tables. Table 27 in the outline of the ISS (see Appendix 6 of the Briefing Package) provides an example shift table for hematology values. Mean change analyses are not planned for the pooled data since the laboratory data from different studies were obtained from multiple laboratories with varying analytical methods and reference ranges. No safety signals regarding laboratory evaluations were detected based on previous comprehensive analyses of laboratory data from individual studies.*

*Does the Agency agree with the proposed approach for presentation of Clinical Laboratory Evaluations?*

**Response:**

*Your proposed approach is reasonable. You should also include an outlier analysis for abnormal laboratory values.*

**15. ISS – ECG Data**

*In in vitro and in vivo pharmacology experiments in addition to ECG monitoring in toxicity studies, no signal for prolongation of cardiac repolarization has been detected in these nonclinical investigations with roflumilast and its N-oxide metabolite. In a QT/QTc study (BY217/CP-069) in 65 healthy volunteers conducted in accordance with ICH Guidance Topic E14, the effect of gradually increasing doses of roflumilast on cardiac repolarization was evaluated in comparison to placebo and no statistically significant findings were seen.*

*In the proposed ISS (see Appendix 6 of the Briefing Package), ECG data (section 4.2 of the ISS) will be presented as an integrated narrative discussion of all ECG findings, with focus on study BY217/CP-069. Other roflumilast studies in which ECG data were collected will also be included in the submission and undergo careful evaluation and study-to-study comparisons. The ECG data from these various studies will not be pooled based on differences in study design and methods of capturing and evaluating these study data.*

*Does the Agency agree that the proposed presentation of ECG data is adequate for review and for decision on approval of the roflumilast tablet NDA?*

**Response:**

*Your proposed approach is reasonable. You should also include an outlier analysis for abnormal ECG findings.*

**16. Safety Information in the Labeling**

*In accordance with the Guidance for Industry “Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” dated January 2006, the sponsor proposes to base the Adverse Reaction Table in the Adverse reactions section of the labeling on the two pivotal studies BY217/M2-124 and -125. In these two trials comparing 500 mcg roflumilast to placebo in patients of the proposed indication, about 3000 patients will be randomized.*

*Does the Agency agree with the proposed approach?*

**Response:**

*While this approach may be reasonable, your clinical development program has a significant safety database beyond your pivotal studies. Determination of the appropriate safety database to use for labeling purposes will be a review issue. Additionally, all adverse events should be reported without ascertainment of relatedness to drug.*

**17. Patient Narratives**

*Based on ICH Guideline Topic E3, stating that cases that are clearly unrelated to the test drug do not have to be described in narratives, the sponsor intends to provide narratives only for those cases that occurred under treatment with roflumilast, i.e., to omit all SAEs and other significant AEs that occurred under treatment with placebo or at baseline. Narratives will not be provided for all the non-fatal COPD exacerbations. As the proposed indication is in COPD patients; for all non-COPD trials, narratives will be provided only for deaths and AEs (SAEs and non-serious AEs) of special interest.*

*There will be narratives describing (see Table 2.2):*

**1. Deaths**

*All deaths, in subjects exposed to roflumilast in all studies, will be described in narratives.*

**2. Other Serious Adverse Events**

*All non-fatal SAEs in subjects exposed to roflumilast in COPD studies will be described in narratives. Narratives will not be provided for non-fatal COPD exacerbations. In addition, non-fatal SAEs of topics of interest (Weight decrease, Infections (TNF-alpha Inhibition), Tumors (TNF-alpha inhibition), Mesenteric Vasculitis, and Cardiac Safety (see Question 13)) in subjects exposed to roflumilast in non-COPD studies will be described in narratives.*

**3. Treatment discontinuation due to an adverse event in COPD studies**

*All patients who were on any dose of roflumilast in COPD studies and discontinued treatment as a result of an adverse event will have a narrative. Narratives will not be provided for non-fatal COPD exacerbations.*

**4. Significant Adverse Events judged to be of Special Interest in all studies**

*Narratives will be provided for SAEs and non-serious AEs based on their medical relevance to the topics of interest in subjects exposed to roflumilast in all studies. Topics of interest are Weight decrease, Infections (TNF-alpha Inhibition), Tumors (TNF-alpha inhibition), Mesenteric Vasculitis and Cardiac Safety (see Question 13).*

*The narratives writing will follow the ICH Guideline Topic E3.*

**Table 2.2: Submission of Narratives**

	<i>Category of Adverse Events</i>				
	<i>Deaths*</i>	<i>Non-fatal SAEs*,**</i>	<i>Withdrawals due to AEs*,**</i>		<i>Significant nSAEs*,***</i>
			<i>SAE</i>	<i>nSAE</i>	
<i>COPD studies</i>	X	X	X	X	X
<i>non-COPD studies</i>	X	X***	-	-	X

*SAE = Serious Adverse Event, nSAE = non-serious Adverse Event*

\* *Exclude placebo and baseline events*

\*\* *Exclude COPD exacerbations*

\*\*\* *Restricted to topics of interest: Weight decrease, Infections (TNF-alpha Inhibition), Tumors (TNF-alpha inhibition), Mesenteric Vasculitis and Cardiac Safety (see Question 13)*

*Does the Agency agree with the proposed approach?*

**Response:**

*We agree.*

#### 18. Case Report Forms

*Case Report Forms will be provided for all cases for which narratives will be provided (see Question 17).*

*Does the Agency agree with the proposed approach?*

**Response:**

*We agree.*

**Discussion:**

- Nycomed indicated that the initial questions did not specifically address Phase 1 and studies conducted in Japan. Safety information for SAEs reported will be available within each study report, but they do not plan to provide additional narratives and CRFs for Phase 1 and studies conducted in Japan.

➤ The Division found the proposal acceptable. The Division asked that this safety information from the Phase 1 and Japanese studies be summarized in the ISS.

**19. Datasets of Efficacy/Safety Trials**

*With the roflumilast tablet NDA, datasets will be provided for efficacy/safety clinical studies (summarized in the ISE and ISS as well as in sections 2.7.3 and 2.7.4 of the CTD) as listed below.*

*The Applicant intends to submit study-wise efficacy SDTM-formatted datasets for the pivotal COPD studies (BY217/M2-124 and -125) as well as for the studies included into the 6-month studies pool (Studies BY217/FK1 101, BY217/FK1 103, BY217/M2-107, -110, -121, -127, -128) and for the M2-111+M2-112 pool.*

*In terms of analysis datasets, ADaM-formatted datasets will be provided for the lung function and COPD exacerbation domains. Furthermore, the sponsor intends to submit integrated ADaM-formatted datasets for each of the efficacy study pools addressing lung function and COPD exacerbation domains.*

*SDTM-formatted safety datasets will be provided for each study of the pivotal COPD studies pool (BY217/M2-124 and -125) and the COPD safety pool (BY217/FK1-101, -103 (without withdrawal arm), BY217/M2-107, -110, -111, -112, -118, -119, -121, -124, -125, -127, -128, BY217/IN-108).*

*For placebo-controlled studies conducted in the indication asthma included in the asthma safety pool (BY217/FK1-003, -004, -011, -020, -021, BY217/FHP-031, BY217/M2-012, -013, -014, -023) datasets of the following safety domains will be submitted: trial design specification, demographics (including weight decrease), adverse events, laboratory data, exposure time, vital signs, ECG, medical history, previous and concomitant medication.*

*Furthermore, integrated safety ADaM-formatted datasets for each safety pool will be provided (pivotal COPD studies pool, COPD safety pool, and asthma safety pool) where SDTM-formatted datasets are not sufficient to support analyses.*

*Does the Agency agree with the proposed approach?*

**Response:**

*1. Our review of the efficacy will be based on all COPD studies (4 one-year studies and 7 six-month studies).*

**Discussion:**

- Nycomed requested clarification on whether SDTM and ADaM formatted datasets from placebo-controlled asthma trials are necessary for submission with the NDA.

- The Division responded that we prefer that Nycomed include all safety information, and therefore, requested that ADaM formatted datasets from placebo-controlled asthma trials be submitted.

*2. Submit efficacy and safety SDTM-formatted datasets for all COPD studies (4 one year studies and 7 six months studies).*

*3. In terms of efficacy analysis datasets, submit ADaM-formatted datasets for each individual study. For the integrated ADaM-formatted pooled datasets, include the study number.*

**Discussion:**

**These discussions pertain to Question 19 Response 3 and Question 32 (a) Response 2 regarding submission of ADaM-formatted datasets for each individual study.**

- Nycomed proposed not to submit ADaM-formatted datasets for each individual study since all information will be included in the pooled ADaM-datasets. Based on these pooled ADaM-datasets, all clinical efficacy and safety endpoints of the single studies can be recalculated.
- The Division stated that the strategy is acceptable. The Division clarified that the datasets would contain the necessary information which could be extracted without further analysis required.
- This was confirmed by Nycomed.

**20. Studies conducted in Japan**

*Studies conducted in Japan will be presented in Module 5. In accordance with ICH Guideline Topic E3, the sponsor proposes to provide English translations of sections 1-16.1 of the Japanese study reports.*

*Does the Agency agree with the proposed approach?*

**Response:**

*We agree.*

**Discussion:**

- Nycomed indicated that the initial question referenced providing information for studies conducted in Japan up to and including section 16.1 associated with the ICH E3 format of clinical study reports. However, Nycomed only intends to provide English translations and the original Japanese study report up to section 16.1.1 Protocol and Protocol Amendments, other sections of 16.1 will not be included.

➤ The Division found the proposal acceptable.

**21. Statistical Analysis Plan (SAP) of Pivotal Studies**

*The study designs of the pivotal studies BY217/M2-124 and BY217/M2-125 are almost identical. The draft Statistical Analysis Plan of study BY217/M2-125 (which will be similar to the SAP of BY217/M2-124) is provided in Appendix 8 of the Briefing Package.*

*Does the Agency agree with selection of the primary analyses and that the proposed approach provides an adequate analysis of the data of the pivotal trials to support a decision on approval of roflumilast tablets in the proposed indication?*

**Response:**

1. *Your pre-specified primary efficacy analyses seem appropriate.*
2. *In addition to your proposed analyses, provide the K-M curves of time to dropout, time to first exacerbation, and time to death by treatment with patient count at each time point.*
3. *At this time, we have no comment on the draft SAP for Study 217/M2-125.*

**22. SAP for the ISE**

*The draft SAP for the ISE is provided in Appendix 5 of the Briefing Package.*

*Is the Agency in agreement that the scope and methods of planned analyses in the draft SAP will allow for an adequate analysis of the efficacy data?*

**Response:**

*We expect that you have incorporated the statistical method and data handling approaches that have been submitted for review into the study protocols. The technical details of the SAP will be reviewed when the NDA is submitted.*

**23. SAP for the ISS**

*The draft SAP for the ISS is provided in Appendix 7 of the Briefing Package.*

*Is the Agency in agreement that the scope and methods of planned analyses in the draft SAP will allow for an adequate analysis of the safety data?*

**Response:**

*We expect that you have incorporated the statistical method and data handling approaches that have been submitted for review into the study protocols. The technical details of the SAP will be reviewed when the NDA is submitted.*

**Discussion:**

- With regard to questions 21 through 23, Nycomed indicated that they plan to submit final SAPs for pivotal trials and the integrated analyses to the IND, prior to unblinding of the pivotal trials. Nycomed indicated that they would like to submit the SAPs in June 2008, and stated that their data lock will be sometime in July. They asked if the Division would be able to provide feedback if the SAP is submitted in June.
- The Division indicated that since the protocols have been submitted and reviewed, there is no need to review the SAPs. However, if Nycomed thinks that there are major deviations in statistical methods and data handling approaches in the SAP from the study protocol, they should submit the SAPs and indicate in the cover letter that there are major differences in statistical methods between the SAPs and the protocols. In case the SAPs need to be reviewed because of major deviations from the study protocol, the Division recommended that Nycomed delay the lock of database until receiving feedbacks from the agency.

**Regulatory**

**24. Organization of Module Table of Contents**

*Section 3 of the Briefing Package includes the proposed Table of Contents for Modules 1 – 5 of the eCTD.*

*Does the proposed Table of Contents for Modules 1 – 5 fulfill the requirements of the Agency reviewers?*

**Response:**

*Yes, the proposed Table of Contents for Modules 1-5 is adequate.*

**Question 25: Financial Disclosure**

*Module 1 section 1.3.4 of the eCTD will include Financial Disclosure/Certification information for covered studies in accordance with 21 CFR 54. The studies for which Financial Disclosure/Certification will be provided are the two pivotal studies BY217/M2-124 and -125 since these are the studies investigating the effectiveness and safety of roflumilast in the population of the proposed indication.*

*Does the Agency agree with the proposed approach?*

**Response:**

*We do not agree. Provide Financial Disclosure/Certification for the pivotal studies as well as the supportive studies.*

**Discussion:**

- Nycomed indicated that they will provide financial disclosure information from COPD specific studies as follows:
  - Pivotal: M2-124, M2-125
  - Supportive: M2-111, M2-112, FK1-101, FK1-103, M2-107, M2-110, M2-121, M2-127, M2-128 .

➤ The Division found the proposal acceptable.

**26. Pediatric Research Equity Act (PREA) Requirements**

*Reference is made to the minutes of the COPD pre-IND meeting for roflumilast held on October 5, 2000. In the minutes dated November 7, 2000, the Division stated*

*“It would be appropriate to give a waiver for pediatric studies for a COPD drug”.*

*Therefore, the sponsor considers that no pediatric studies are required for roflumilast tablets for the proposed indication “maintenance treatment of patients with severe COPD associated with chronic bronchitis for the reduction of COPD exacerbations” and PREA requirements are fulfilled. The sponsor will request a waiver for pediatric studies (all paediatric age groups) in Module 1 of the NDA.*

*Does the Agency agree?*

**Response:**

*Yes, we concur that a waiver may be appropriate. If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver when submitting your NDA application. Include supporting information and documentation in accordance with the provisions of 21 CFR 314.55. You may find more information on CDER's Pediatric Drug Development Page (<http://www.fda.gov/www.fda.gov/cder/pediatric/>) and in the Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act (<http://www.fda.gov/cder/guidance/6215dft.pdf>).*

*eCTD Content, Organization and Electronic Format*

**27. Study Tagging Specifications for Study Reports**

*All study reports in Module 4 and Module 5 will be submitted as legacy reports with the exception of the reports of the two pivotal studies BY217/M2-124 and BY217/M2-125 and of the supportive COPD studies BY217/FK1 101, BY217/FK1 103, BY217/M2-107, -110, -111, -112, -118, -119, -121, -127, -128 and BY217/IN-108. All reports will be added to the eCTD with STF (i.e., include an stf.xml file), however, only for the two pivotal studies and for the supportive COPD studies the reports will be study tagged (see Appendix 9, CD-ROM). These reports are paginated as a complete study report from page 1, the title page through Appendix 16.4. The individual files of the study reports are not paginated individually.*

- a. *Is the approach of study tagging only the listed clinical study reports acceptable?*

**Response:**

*Your approach is acceptable.*

- b. *Is the lack of individual file pagination acceptable?*

**Response:**

*Yes, this is acceptable.*

**28. Location of Datasets and CRFs and narratives**

*As described in Sections 8.6.2 to 8.6.4 of the Electronic Submission Plan (see Section 8 of the Briefing Package), the sponsor plans to study tag the CRFs, narratives and datasets.*

*CRFs will be provided within a directory labeled "crfs" within each respective study folder. Additionally, the crf folder will be divided by each study site (please refer to Section 8.6.3 of the Electronic Submission Plan for a sample directory structure). The CRFs will be referenced in Section 5.3.7 Case Report Forms and Individual Patient Listings in the eCTD, as per ICH Guidance M4: The eCTD – Efficacy Question and Answer, revision 3.*

*Narratives are provided for selected cases (see Question 17) and will be placed directly after the corresponding study report and before the CRFs and datasets within the eCTD structure. Additionally these files are tagged appropriately (as "subject profile") and the actual document would then be found in the study report specific folder (for details see Section 8.6.3 of the Electronic Submission Plan). In addition a table of contents including the category of the adverse events will be included in section 5.7.6 "Case Report Forms and Individual Patient Listings" of the eCTD (narrativetoc.pdf).*

*The location of the datasets can be found within each respective study folder in a directory labeled “datasets.” Subfolders titled “analyses” and “tabulations” will contain the ADaM and SDTM datasets, respectively. A sample of the directory structure for the datasets is located in Section 8.6.4 of the Electronic Submission Plan.*

*For details see Appendix 9.*

- a. *Is the location and directory structure of the CRFs and datasets acceptable?*
- b. *Is the Agency in agreement that CRFs can be reviewed by way of hyperlink from the patient narrative and from the STF in the CSR?*
- c. *Is the integration of the individual narratives into the eCTD structure acceptable?*

**Response:**

*Yes, all of the above are acceptable.*

#### **29: Format of Pharmacokinetic Datasets**

*With the NDA, pharmacokinetic data (plasma concentration and derived variables such as AUC, Cmax, etc.) will be provided for each individual pharmacokinetic study as CSV (comma separated values), Pharsight working object (PWO) and Pharsight model object (PMO) files. A define.xml file will be provided, whereas a define.pdf file will not be provided. Data for the population pharmacokinetic (Pop-PK) analysis will be provided in NONMEM format together with a description of the data files (CSV) and the NONMEM control streams.*

*Does the Agency agree with the proposed approach?*

**Response:**

*No, we do not agree. All pharmacokinetic data should be submitted as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file.*

*For Pop-PK, all datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt). A model development decision tree and/or table which gives an overview of the modeling steps should be provided.*

**30: Sample Clinical Datasets**

*Sample datasets from a clinical study (study BY217/M2-127) have been provided in Appendix 9 (CD-ROM) of the meeting Briefing Package, which includes data in SDTM and ADaM format, as well as define.xml file and an associated style sheet.*

*Does the Agency agree with the proposed approach of dataset submission, as illustrated by the provided sample datasets?*

**Response:**

*We agree. The dataset with SDTM and ADaM format are acceptable.*

**31: Patient Profiles**

*It is assumed that the Agency has appropriate tools that can generate patient profiles from datasets provided from a Sponsor if the datasets are in CDISC format. The Sponsor will be providing datasets in CDISC – SDTM format, therefore, the Sponsor is requesting a waiver for patient profiles.*

*Does the Agency agree with a waiver for patient profiles?*

**Response:**

*We do not agree with a waiver for patient profiles. Provide patient profiles for SAEs and deaths with your NDA submission. We may request other patient profiles as necessary during the review process.*

**Discussion:**

- Nycomed requested further clarification on the request for patient profiles.
  - The Division asked if Nycomed could provide the approximate number of non-fatal SAEs and deaths in their clinical development program.
- Nycomed indicated that they have a total of about 1500 SAEs, with about 200 fatal outcomes. Nycomed indicated that their intention is to provide the data on the COPD trial and placebo-controlled trials. They also intend not to submit the asthma data nor any data from Japan. Nycomed asked if this was acceptable.
  - Based upon the information regarding the number of SAEs and deaths, the Division requested that Nycomed submit the patient profiles for deaths. .

**32: Statistical Programming Code**

*The sponsor intends to submit SAS programming code for all primary and key secondary measures for the pivotal studies BY217/M2-124 and -125.*

*Furthermore, the SAS programming code of the integrated analyses of the lung function and COPD exacerbation variables of the pivotal COPD studies pool, M2-111+M2-112 pool and the 6-month studies pool (Studies BY217/FK1 101, BY217/FK1 103, BY217/M2-107, -110, -121, -127, -128) will be provided. The sponsor intends to provide SAS programming code under the dataset directory “analyses/programs” for each study referenced above. They will be provided in pdf and ASCII format.*

- a. *Does the FDA wish to receive the programming code for statistical analyses performed?*

**Response:**

*Yes.*

*1. Provide the SAS programming codes which can run on the submitted datasets and can re-produce the analysis results in the study reports.*

*2. Provide the SAS programming code for creating analysis dataset (ADaM-format) for all efficacy studies.*

**b. *If so, is it acceptable to submit only the SAS code used to analyze the primary and key secondary measures of the pivotal trials?***

**Response:**

*1. Submit the SAS code for primary and secondary measures for all COPD studies.*

*2. Provide the SAS programming code for statistical safety analysis.*

*3. Make programs for other analyses available upon request.*

**c. *Does the agency agree with the approach regarding the SAS programming code of the integrated analyses?***

**Response:**

*The Demo CD-ROM did not include the SAS programming code of the integrated analyses.*

**d. *Is the location and format of the programs identified acceptable?***

**Response:**

*Yes. In addition, provide the documentation to describe the usage of each SAS program.*

**Additional Clinical Comments:**

*We note that there are few results reported from your clinical development program in this pre-NDA meeting package. Without results from your Phase 3 program, we are unable to provide general comments on the adequacy of your program to support the proposed indication(s) or labeling claims.*

*We acknowledge your definition of exacerbations based on requirement of oral or parental glucocorticoids and/or hospitalization. The acceptability of your definition of exacerbation will be a review issue. Further, in the ISE, we request that you provide an analysis of respiratory events that required antibiotics for each of your phase 3 trials, as treatment with antibiotics may also identify exacerbations.*

*Your NDA submission should discuss and provide justification for the minimal clinically important difference in trough FEV1 between active treatment with roflumilast and placebo.*

#### **Discussion:**

#### **Definition of Exacerbations**

- Nycomed indicated that the definition of exacerbations in M2-124/-125 is in accordance with the Division's recommended definition described within a communication dated November 2, 2005 (M2-111 protocol assessment) and February, 12, 2007 (Response to Type C meeting Request).
  - The Division acknowledged this previous correspondence, but further explained that there is no consensus definition of a "COPD exacerbation" presently. The definition of exacerbation is in evolution, and as a result the Division continues to modify its thinking based on emerging issues, such as those identified within the TORCH study and the ensuing advisory committee discussion. The Division acknowledged that the start of the roflumilast program pre-dates many of the current discussions regarding COPD exacerbations, however, comparisons to recent programs (i.e. TORCH) will be inevitable. Thus the Division suggested that it would be in Nycomed's best interest to address these issues prospectively, as they would be likely to come up during an advisory committee discussion regarding their application. To get a sense of the current issues surrounding COPD exacerbations, the Division suggested that Nycomed refer to other COPD trials to get a sense of what others have done, what the Division has required, and what the shortcomings have been. The Division also clarified that in addition to the primary endpoint of exacerbation, we would also examine the time to exacerbation and duration of exacerbation as secondary endpoints.

### **Analysis of Respiratory Events**

- Nycomed requested clarification of the statement “Further, in the ISE, we request that you provide an analysis of respiratory events that required antibiotics for each of your phase 3 trials.” Nycomed proposes to conduct an analysis of COPD-exacerbations that required antibiotics as an additional secondary endpoint in all four 1 year trials M2-111/-112/-124/-125 and respective defined pooled analyses. Nycomed does not intend to conduct this analysis with the supportive trials of 6-month duration.

➤ The Division found the proposal acceptable.

### **Tradename:**

- The Division asked that Nycomed provide proposed tradenames for this application. The Division noted that DAXAS has been used throughout the Pre-NDA package but this name was never formally submitted for review.
  - Nycomed indicated that they will provide a name for review. Nycomed indicated that they plan to submit the NDA for COPD by March 2009.

Drafted by: LJ/4-18-08

Initialed by: Pei/4-24-08  
McGovern/4-24-08  
Li/4-18-08  
Karimi-Shah/4-25-08  
Seymour/4-25-08  
Chowdhury/4-28-08

Filename: I57883mtgmin.doc

Linked Applications

Sponsor Name

Drug Name

IND 57883

NYCOMED GMBH

ROFLUMILAST 0.25MG/0.50MG TABLETS

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

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/s/

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LADAN G JAFARI

04/28/2008

IND 57,883  
Sponsor: Byk-Gulden/Altana  
Drug: roflumilast  
Indication: COPD  
End of Phase 2 meeting: December 6, 2001

**Byk-Gulden Representatives:**

Robert Anderson, Senior Director, Scientific Affairs, Altana  
Dirk Bredenbroeker, Director, Medical Research Pulmonology, Byk-Gulden  
Cindy Dye, Regulatory Associate, Altana  
Susanne Heiland, Regulatory Project Manager, Byk-Gulden  
Joerg Kemkowski, Senior Research Scientist, Toxicology, Byk-Gulden  
Karl Zech, Director, Drug Metabolism & Pharmacokinetics, Byk-Gulden  
Mohamed Baccouche, Vice President, International regulatory Affairs, Byk-Gulden

**Division of Pulmonary & Allergy Drug Products (DPADP):**

Young-Moon Choi, Clinical Pharmacology & Biopharmaceutics Reviewer  
Emmanuel Fadian, Clinical Pharmacology & Biopharmaceutics Team Leader  
Jim Gebert, Biometrics Team Leader  
Lydia Gilbert-McClain, Clinical Reviewer  
Ladan Jafari, Regulatory Project Manager  
Tim McGovern, Preclinical Reviewer  
Robert Meyer, Director  
Prasad Peri, Chemistry Reviewer  
Mary Purucker, Clinical Team Leader

**Background:** Byk-Gulden/Altana submitted an End of Phase 2 meeting request to discuss the development plan for roflumilast for COPD indication. (See attachments 1,2, and 3 for Drs. McGovern, Choi, and Gilbert-McClain's slides.)

**CMC:**

Byk-Gulden asked for the Division's comments on the shape, size, and debossing of the tablets. The Division noted that the to-be marketed product is different in shape from the tablets used in the pivotal clinical trials. The following information will also be required at the time of NDA submission.

1. 6-month accelerated and available long-term stability data.
2. Comparative stability data of the round (b) (4) shape of the tablets to assess the physico-chemical parameters of the drug product (e.g., hardness, moisture, dissolution profile, friability.)
3. Comprehensive and adequate stability protocol.
4. The to-be marketed tablet should not be identical to any approved drug product on the market.

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**Pharmacology/Toxicology:**

Byk-Gulden asked for the Agency's agreement that initiation of two US Phase 3 COPD trials with a treatment duration of 24 weeks is acceptable based upon the data of the 12-month dog study with Roflumilast N-oxide and the safety assessment included in the background package. The Division referred to the following issues discussed at the Pre-IND meeting dated October 5, 2000, and a subsequent teleconference in May, 2001.

1. A one-year dog study with roflumilast should be submitted prior to or at the time of clinical trial initiation and a one-year dog study with Roflumilast N-oxide should be submitted prior to initiation of the COPD trials.
2. An adequate safety margin is not present to conduct the proposed trials at a dose of 500 mcg, due to male reproductive organ toxicity in rats.
3. Inclusion of a statement in the Informed Consent regarding the positive carcinogenic findings of a compound that is structurally similar to roflumilast.
4. Increased systemic exposure in elderly patients should be considered when selecting doses for COPD trials.

The Division stated that the following comments were based upon a preliminary review of the 12-month studies in dogs with Roflumilast and Roflumilast N-oxide. Currently, non-clinical data support dosing up to 250 mcg in younger female subjects in the proposed 6-month COPD trial. However, this dose is not currently supported in males due to spermiogenic findings in the 12-month dog study with roflumilast N-oxide (i.e., sperm neck alterations, eosin staining) that resulted in a NOAEL dose of 0.1 mg/kg in males. In addition, the non-clinical data in rats and dogs do not support dosing at 250-500 mcg in older patients who would be enrolled in the COPD trial. The Division reiterated that because there is increased systemic exposure in older patients, we remain concerned with dose selection in COPD trials.

Byk-Gulden indicated that they have historical data from animals that would alleviate the concern for spermiogenic findings. In addition, the sponsor will investigate discrepancies in eosin staining data between the submitted report and data presented at the meeting.

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The Division indicated that based upon our review, the NOAEL dose for males in the 12-month dog study with Roflumilast N-oxide is 0.1 mg/kg, and asked that Byk-Gulden submit historical data to support their claim that findings for neck alterations fall within normal range. The Division stated that the identified NOAEL dose could be increased based upon evaluation of the additional data. Additionally, negative results in the sponsor's clinical trial assessing spermiogenic effects could offset concerns raised in the animal study.

The Division also discussed Byk-Gulden's recent submission concerning summaries of the mouse and hamster carcinogenicity studies. The Division indicated that the nasal tumors observed in the hamster study are considered likely related to the nasal toxicity found in rodents. However, further review of the studies, as well as consultation with the Agency's Carcinogenicity Assessment Committee, is needed to confirm that the tumor findings in hamsters are irrelevant to humans.

Byk-Gulden indicated that they are currently preparing additional data to support the position that the male reproductive organ findings in non-clinical studies are not relevant to humans. The data will include a 4-week dose range study in monkeys, a 6-month mouse study, a hormone study in rats and a 4-week study in healthy volunteers. The sponsor asked if the submission of these data could affect the dose limitations due to the male reproductive organ toxicity.

The Division stated that any additional data would be considered in determining the relevancy of the toxicity to humans and the current identification of the rat as the most appropriate species to calculate a clinical safety factor.

#### **Clinical Pharmacology & Biopharmaceutics:**

Byk-Gulden asked about any bioequivalence study requirements and the Division responded that the current acceptable bioequivalence criteria for AUC and  $C_{max}$  is 0.8-1.25 of the 90% confidence interval of the T/R ratio. The Division also indicated that the comparative dissolution profiles should be generated for all strengths at least at three pH levels (1, 4.5 and 6.8).

Byk-Gulden asked if they need to obtain the  $C_{max}$  and AUC for roflumilast only or for both the active ingredient and the active metabolite. The Division stated that because roflumilast is highly metabolized to an active metabolite, the pharmacokinetic information for both the parent and active metabolite should be obtained. For the same reason, the Division also recommended that the pharmacokinetics of the parent and active metabolites be studied in moderately and severely hepatically impaired patients.

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**Clinical/Statistical:**

Byk-Gulden asked for the Division's comments on protocols BY217/M2-106, M2-107, and M2-110. Byk-Gulden also asked for the Division's comments regarding primary and secondary endpoints, inclusion and exclusion criteria, and the treatment duration chosen regarding the approval of roflumilast. The Division indicated that although the change in FEV<sub>1</sub> is a reasonable endpoint, because the change seen was very small, supportive evidence is needed with the secondary endpoints. The Division referred Byk-Gulden to the Pre-IND meeting minutes for endpoints.

The Division stated that the proposed Phase 3 COPD studies BY217/M2-106, M2-107, M2-110 are all acceptable in design for a general indication for COPD maintenance therapy, however, several labeling claims are not supported by the protocols as outlined below:



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(b) (4)

The Division discussed study FK1 103 and indicated that it would not be considered as a pivotal study but should be submitted as one of the supporting studies of efficacy.

In addition, the Division stated that Byk-Gulden should measure  $QT_c$  interval and obtain ECGs at  $C_{max}$  and steady state. Byk-Gulden indicated that they planned to obtain ECGs at steady state and not at  $C_{max}$ . The Division asked that Byk-Gulden include ECGs at  $C_{max}$  and steady state for both the active ingredient and the active metabolite for Phase 3 studies.

The Division reiterated that we remain concerned with both doses in asthma studies, however, for COPD patients, the Division may consider allowing the use of the 500  $\mu$ g dose but this decision would require further internal FDA discussion.

**Regulatory:**

Byk-Gulden asked if they should submit an ISE and ISS with a CTD document for roflumilast NDA. The Division responded that we expect a CTD together with an ISE and ISS.

Byk-Gulden asked if they could get the Agency's acceptance of a trade name prior to filling the NDA. Byk-Gulden indicated that their application in Europe will be under way sooner than it would be in the United States and they want to make sure that they could have the same name universally. The Division indicated that no decision is final until the NDA is approved. The Division stated that Byk-Gulden could submit up to 2 trade names with preliminary labeling to the Office of Drug Safety [formerly OPDRA] from the Pre-NDA stage on, however, no decision is final until the NDA is approved.

Byk-Gulden asked if they could request a priority review for this application since it addresses an unmet medical need. The Division indicated that Byk-Gulden could make such request but it needs to be supported with an appropriate rationale. The determination of suitability for a priority review is made after the NDA submission.

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Attachment 2:

**IND 57,883 (Serial No. 138)**

**Clinical Pharmacology and Biopharmaceutics**

**Q1.** The tablets to be used for marketing will be different from those used in the pivotal clinical studies.

The shape of the tablets will be changed from round to (b) (4) and the amount of excipients will be (b) (4) for the 500 microgram tablet.

1. Considering that roflumilast tablets are an immediate release dosage form,
2. Assuming that study (b) (4) will prove bioequivalence of the to-be-marketed tablet and round tablet produced at (b) (4), and
3. Assuming that the in vitro dissolution profiles are similar,

No further bioequivalence study will be conducted. Do you agree?

**Agency's response:**

**Yes.**

The sponsor should be aware that the current acceptable bioequivalence criteria for C<sub>max</sub> is 0.8 – 1.25 of the 90% confidence interval of the T/R ratio.

The dissolution profiles should be generated for all strengths. The drug similarity is based on the f<sub>2</sub> values in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8).

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Initialed by: McLain/1-2-02  
Purucker/1-2-02  
McGovern/1-3-02  
Sun/1-3-02  
Choi/1-2-02  
Peri/1-4-02  
Fadiran/1-2-02  
Meyer/1-4-02

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/s/

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Ladan Jafari  
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