# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022522Orig1s000

# CHEMISTRY REVIEW(S)

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

**DATE:** 23-FEB-2011

**TO:** N22522 File

**FROM:** Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

**THROUGH:** Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

**SUBJECT:** Office of Compliance Recommendation and overall CMC Recommendation

**RECOMMENDATION:** After the fifth CMC review dated 08-NOV-2010, the CMC recommended that the application was approvable due to the pending recommendation from the Office of Compliance. There had been one outstanding inspection at that time. The Office of Compliance has now provided on 22-FEB-2011 in the Establishment Evaluation System, an ACCEPTABLE recommendation for the application. As such, the CMC team now recommends that the application be **approved.**

_____
Craig M. Bertha, Ph.D.
Chemist

cc:
OND/DPARP/CHill
ONDQA/DIV 1/CBertha/23-FEB-2011
ONDQA/DIV 1/PPeri_____
ONDQA/DIV1/ASchroeder
OND/DPARP/ADurmowicz

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/s/

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CRAIG M BERTHA
02/23/2011

PRASAD PERI
02/23/2011
I concur

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

**DATE:** 10-FEB-2011

**TO:** N22522 File

**FROM:** Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

**THROUGH:** Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division III, Branch VIII

**SUBJECT:** Removal of agreement to revisit and modify the drug substance particle size distribution (PSD) acceptance criteria post approval

**BACKGROUND:** The roflumilast drug substance has poor solubility in water, thus the applicant uses micronized drug substance to prepare the drug product. As such, they test the micronized drug substance by laser diffraction methodology to determine the PSD, and they have set acceptance criteria for this test, consistent with the principles of ICH Q6A. The drug substance PSD acceptance criteria proposed in the original application were considered to be broad relative to the historical data presented in the application. The acceptance criteria originally proposed were:

(b) (4)

However, in addition to the historical PSD data, the applicant did demonstrate (see p. 76 of CMC review #1) that they could prepare a batch of drug product with a drug substance batch having generally larger particle sizes (b) (4) than typical, and still achieve drug product with acceptable *in vitro* dissolution. The applicant was asked to either tighten the acceptance criteria to reflect their typical data or to provide additional data demonstrating that drug substance of the maximum particle size allowed by the acceptance criteria produces drug product with acceptable dissolution. The applicant responded but did not provide additional data in support of the proposed PSD acceptance criteria. Their whole argument for not changing the PSD acceptance criteria hinged on the data from that single batch of drug substance with a particle size distribution closer to the acceptance criteria limits. It was decided that since the dissolution was dependent on the drug substance particle size, and all batches would need to pass the dissolution testing to be released, the applicant would be asked to agree to revisit the drug substance PSD acceptance criteria once they have prepared a sufficient number of commercial batches that have been used to prepare acceptable drug product batches. They agreed 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.*

However, it was brought to the attention of the CMC team that it was not appropriate to obtain such agreements under the new review framework, and the applicant would need to consider this agreement in a more formal fashion as a post marketing commitment (PMC), i.e., with a specific agreed amount of data being provided in an agreed amount of time. A communication dated 21-JAN-2011, was sent which contained the following request:

> *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.*

The 08-FEB-2011, response from the applicant does not provide the PMC that was requested, but does include a revision of the drug substance particle size specification to the following:

(b) (4)

**EVALUATION:** Albeit limited, considering the data that had been provided in the original application for the batch of drug substance having a (b) (4), that was converted into drug product that had acceptable *in vitro* dissolution, and that all drug product batches are tested for dissolution before release, the above tightened acceptance criteria are sufficient and it is no longer necessary for the applicant to include a PMC in the application for revisiting these criteria.

**RECOMMENDATION:** NAI

_____
Craig M. Bertha, Ph.D.
Chemist

cc:
OND/DPAP/CHill
ONDQA/DIV 1/CBertha/10-FEB-2011
ONDQA/DIV 1/PPeri_____
ONDQA/DIV1/ASchroeder
OND/DPARP/SSeymour

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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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CRAIG M BERTHA
02/10/2011

PRASAD PERI
02/10/2011
I concur

# TRADENAME (roflumilast) Tablets
## NDA 22-522

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

**Applicant:** Forest Research Institute, Inc.
(originally filed under Nycomed, Inc.)
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

**Indication:** Roflumilast is an anti-inflammatory agent indicated for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

**Presentations:** Roflumilast tablets are supplied as 500 mcg white round tablets, embossed with "D" on one side and 500 on the other side. DAXAS tablets are available in HDPE bottles with child resistant closure containing 30 tablets or 90 tablets. Roflumilast tablets are also available as a t tablets/per blister card.

**EER Status:** **Pending as of Feb 4, 2010, acceptable previously 27-Aug-2009. Note that the sites were resubmitted when the NDA was resubmitted and Office of Compliance has decided that they should inspect the drug substance micronization site (b) (4) . Although an inspection for the (b) (4) site was scheduled in 3-Sep-2010, no further information on the status of the (b) (4) inspection.**

**Consults:** EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.
Pharmacology/Toxicology –Acceptable (L. Pei)

**Original Submission:** 15-JUL-2009

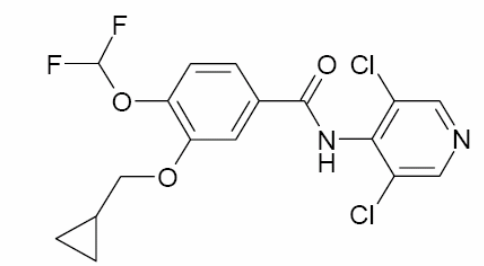
**Post-Approval CMC Commitments:**

The applicant agrees to revisit the drug substance PSD acceptance criteria after preparing multiple (e.g., 10) commercial batches.

**Drug Substance:**

The drug substance roflumilast is described as a white to off-white powder with the following IUPAC name: 3-(Cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22. It is an anti-inflammatory agent and a selective phosphodiesterase 4 (PDE4) inhibitor. The

compound is practically insoluble in water and hexane, sparingly soluble in ethanol and freely soluble in acetone. The use of (b) (4) enhances the solubility of the drug substance in water. The pH of the saturated solution in water is 6.35. The drug substance is non-hygroscopic and a polymorph screen identified only a single polymorphic form.



The drug substance is manufactured at the following two sites: Nycomed GmbH, Germany and (b) (4) The drug substance is produced from a (b) (4) The manufacturing process description for the drug substance synthesis was described in the application and critical process steps and critical process parameters were identified. The drug substance is micronized to a defined particle size distribution for formulation, due to the relatively low water solubility (0.52-0.56 mg/L at 21-22°C). The drug substance micronization site is (b) (4).

Structural elucidation was provided by elemental analysis, UV, IR, NMR, Mass Spectroscopy and single crystal X-ray crystallography. The drug substance specification includes Identity (IR, HPLC), Related Substances (HPLC), Residual Solvents (headspace GC), Water Content (Karl Fischer), Sulfated Ash, Heavy Metals, Particle Size Distribution (laser diffraction), and Assay/Content (HPLC, titration). A retest period of (b) (4) has been established for the drug substance.

**Conclusion:** The drug substance is satisfactory.

**Drug Product:**

Tradename (roflumilast) tablets and contain 500 mcg roflumilast per tablet. The tablets are uncoated white to off-white round tablets embossed on one side with the letter "D" and on the other side with "500." The relatively small tablets have a diameter of 5 mm and a weight of 66 mg. The trade packages consist of white, rectangular high-density polyethylene bottles with 30 or 90 tablets. There is also unit dose (b) (4) blisters with aluminum foil lidding for use in packaging trade or physician samples. Each blister card contains seven (7) tablets. There is a bulk package that is used for storage and shipping for final packaging. Currently the proposed expiration dating period for the drug product is 24 months, regardless of the package type. The stability data provided support this expiration dating period..

The drug product is manufactured, packaged, released, and stability tested at Nycomed GmbH, Germany. The drug product is also packaged at (b) (4).

The formulation is prepared for tablet compression (b) (4) No steps have been identified in the

manufacturing process that are considered critical in terms of batch reproducibility and product performance, although, roflumilast particle size is important to the attainment of the desired release rate as determined by dissolution testing. A complete manufacturing process description was provided along with suitable in-process controls.


The drug product specifications include testing for Appearance, (b) (4), Identity (UV, HPLC), Identity, Purity (HPLC), Microbial Limits, Content Uniformity (HPLC or UV), and Dissolution. The stability data provided support a 24 month expiration dating period for the bottled and blister packaged drug product.

**Conclusion:** The drug product is satisfactory.

**Additional Items:**

- All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

- The analytical methods used in the testing procedures (release, stability, and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

**Overall Conclusion:**

From a CMC perspective, the application is **approvable, pending a satisfactory recommendation for all manufacturing and testing sites.**

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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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ALI H AL HAKIM
02/04/2011
Ali Al-Hakim acting for Eric Duffy

**CHEMISTRY REVIEW**

# NDA 22522

## Daxas® (Roflumilast) Tablets

## Forest Research Institute, Inc.

**Craig M. Bertha, Ph.D.**
**Office of New Drug Quality Assessment/Division III/Branch VIII**
**for**
**Division of Pulmonary, Allergy, and Rheumatology Products**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 22522

2. REVIEW #: 5

3. REVIEW DATE: 08-NOV-2010

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Amendment | 30-AUG-2010 |
| Amendment | 22-JAN-2010 |
| Amendment | 04-DEC-2009 |
| Amendment | 02-DEC-2009 |
| Amendment | 11-SEP-2009 |
| Amendment | 24-AUG-2009 |
| Original | 15-JUL-2009 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment | 06-OCT-2010 (samples of tablets) |
| Amendment | 28-OCT-2010 (samples of tablets in proposed CCSs) |
| Amendment | 29-OCT-2010 (response to 2nd DR ltr) |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Forest Research Institute, Inc. |
| Address: | Harborside Financial Center, Plaza V<br>Jersey City, NJ 07311 |
| Representative: | Lisa L. Travis, MS, RAC<br>Director Regulatory Affairs |

Telephone: 201-386-2031

## 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Daxas®
b) Non-Proprietary Name (USAN): roflumilast
c) Code Name/# (ONDC only): BYK20869, B9302-107, BY217
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: phosphodiesterase 4 (PDE4) inhibitor (for anti-inflammatory effect)

## 11. DOSAGE FORM: tablet (uncoated immediate release)

## 12. STRENGTH/POTENCY: 500 mcg/tablet

## 13. ROUTE OF ADMINISTRATION: oral

## 14. Rx/OTC DISPENSED: __X_Rx ___OTC

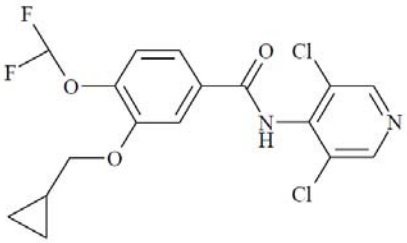
## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

The chemical name of Roflumilast is 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide (IUPAC); or N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide. Roflumilast is achiral and has CAS # 162401-32-3, the following structure, formula, and molecular weight:



| | |
|---|---|
| Molecular formula: | $C_{17}H_{14}Cl_2F_2N_2O_3$ |
| Relative molecular mass: | 403.22 |

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS[3] |
|---|---|---|---|---|---|---|---|
| [redacted] | | | (b) (4) | 3 | Adequate | 18-SEP-2007 | |
| | | | | 3 | Adequate | 12-JAN-2005 | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | See response to DR comment 24 on p. 28 of CR#2 |
| | | | | 4 | N/A | * | As above. |
| | | | | 4 | N/A | | See response to DR comment 3 on p. 10 below |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

[*] Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

**B. Other Supporting Documents:**

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |

**C. Related Documents:**

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|---|---|---|---|
| IND | 57883 | Nycomed GmbH | |

## 18. CONSULTS/CMC-RELATED REVIEWS:

| CONSULTS | SUBJECT | DATE FORWARDED | STATUS/ REVIEWER | COMMENTS |
|---|---|---|---|---|
| Biometrics | N/A | | | See evaluation in P.8., pp.128 and 129 of CR#1, response to comment 25 in CR#2 on p. 28 of CR#2; and evaluation of P.8 in CR#4 |
| EES | PAI | 07 & 10-AUG-2009<br>02-SEP-2010 | ACCEPTABLE<br>Pending | OC decision of 27-AUG-2009<br>Two new sites added |
| Pharm/Tox | BYK20139 impurity allowed to (b) (4) in drug substance<br><br>Residual (b) (4) in drug substance | 03-AUG-2009<br><br>03-AUG-2009 | Final/Dr. Pei<br><br>Final/Dr. Pei | See attachment 1 of CR#1 for structure.<br><br>See p. 53 of CR#1; e-mail from Dr. Pei on 03-DEC-2009 indicates that BYK20139 is of no toxicological concern as it is also a drug metabolite.<br>See p. 68 of CR#1 |
| Biopharm | N/A | | | |
| LNC | N/A | | | |
| Methods Validation | N/A | | | Not deemed necessary, see p. 134 of CR#1; see p. 51 of CR#4 |
| OPDRA | | | | To be forwarded by PM to OSE |
| EA | N/A | | | Categorical exclusion granted, see p. 136 of CR#1 |
| Microbiology | N/A | | | Not needed, see pp. 18, 31, and 37 of CR#4 |

# The Chemistry Review for NDA 22522

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The application is considered **approvable**. The facility inspections are outstanding and the above CMC recommendation does not incorporate any potential facility inspection issues.

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

The applicant provides the following agreement (from the 22-JAN-2010, amendment):

"We herewith agree to revisit the drug substance particle size distribution (PSD) acceptance criteria after we 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."

## II. Summary of Chemistry Assessments

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

The drug product is Daxas® (roflumilast) Tablets and contain 500 mcg roflumilast/tablet. The solid oral dosage form is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The tablets are uncoated white to off-white round tablets embossed on one side with the letter "D" and on the other side with "500." The relatively small tablets have a diameter of 5 mm and weight of 66 mg. The trade packages consist of white, rectangular high-density polyethylene bottles with 30 or 90 tablets. There is also unit dose (b) (4) blisters with aluminum foil lidding for use in packaging trade or physician samples. Each blister card contains seven (7) tablets. There is a bulk package that is used for storage and shipping for final packaging. Currently the proposed expiration dating period for the drug product is 24 months, regardless of the package type. The stability data provided support this expiration dating period.

The formulation of the drug product does not contain any novel or non-compendial excipients and it is prepared for tablet compression (b) (4) No steps have been identified in

the manufacturing process that are considered critical in terms of batch reproducibility and product performance, although, as indicated below, roflumilast particle size is important to the attainment of the desired release rate as determined by dissolution testing. The Formula B tablet is that to-be-marketed and was used in the phase 3 trials.

The drug substance is roflumilast (USAN), a phosphodiesterase 4 inhibitor, and it has a (b) (4) retest period, which is acceptable based on the stability data provided in the application. The drug substance is micronized due to its poor water solubility. It has been found in only a single crystalline form (single polymorphic form) and it is characterized as BCS class 2 (poorly soluble, highly permeable) by the applicant. The particle size distribution of the roflumilast is observed to directly correlate with the dissolution or drug release from the dosage form. The drug substance by itself, and when formulated in the drug product, is observed to have superior chemical and physical stability.

### B. Description of How the Drug Product is Intended to be Used

The 500 mcg tablets are intended for once a day dosing in adults diagnosed with COPD. There are no special storage conditions necessary for the drug product and it is labeled for room temperature storage. A **24 month** expiration dating period is acceptable for the drug product.

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

N/A

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

CBertha/ONDQA/Reviewer/11/08/10
PPeri/ONDQA/DIV III/Acting Branch Chief_____

### C. CC Block

CHill/DPARP/Regulatory PM
PPeri/ONDQA/DIV III/Branch VIII/Acting Branch Chief
ASchroeder/DIV III/Branch VIII/Acting PAL
XHan Sarro/DPARP/Medical Officer
PJi/OCP/Clinical Pharmacologist
MWood/DPARP/Pharmacologist
SSuarez/ONDQA

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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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CRAIG M BERTHA
11/08/2010

PRASAD PERI
11/08/2010
I concur

**CHEMISTRY REVIEW**

# NDA 22-522

## Daxas® (Roflumilast) Tablets

## Forest Research Institute, Inc.

**Craig M. Bertha, Ph.D.**
**Office of New Drug Quality Assessment/Division III/Branch VIII**
**for**
**Division of Pulmonary, Allergy, and Rheumatology Products**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 22-522

2. REVIEW #: 4

3. REVIEW DATE: 13-SEP-2010

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Amendment | 22-JAN-2010 |
| Amendment | 04-DEC-2009 |
| Amendment | 02-DEC-2009 |
| Amendment | 11-SEP-2009 |
| Amendment | 24-AUG-2009 |
| Original | 15-JUL-2009 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment | 30-AUG-2010 |

7. NAME & ADDRESS OF APPLICANT:


| | |
|---|---|
| Name: | Forest Research Institute, Inc. |
| Address: | Harborside Financial Center, Plaza V<br>Jersey City, NJ 07311 |
| Representative: | Lisa L. Travis, MS, RAC<br>Director Regulatory Affairs |
| Telephone: | 201-386-2031 |

Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Daxas®
b) Non-Proprietary Name (USAN): roflumilast
c) Code Name/# (ONDC only): BYK20869, B9302-107, BY217
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: phosphodiesterase 4 (PDE4) inhibitor (for anti-inflammatory effect)

## 11. DOSAGE FORM: tablet (uncoated immediate release)

## 12. STRENGTH/POTENCY: 500 mcg/tablet

## 13. ROUTE OF ADMINISTRATION: oral

## 14. Rx/OTC DISPENSED: __X_Rx ___OTC

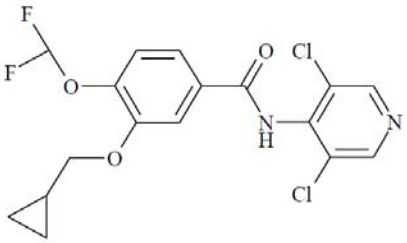
## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

The chemical name of Roflumilast is 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide (IUPAC); or N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide. Roflumilast is achiral and has CAS # 162401-32-3, the following structure, formula, and molecular weight:



| | |
|---|---|
| Molecular formula: | $C_{17}H_{14}Cl_2F_2N_2O_3$ |
| Relative molecular mass: | 403.22 |

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS[3] |
|---|---|---|---|---|---|---|---|
| (b) (4) | | | | 3 | Adequate | 18-SEP-2007 | |
| | | | | 3 | Adequate | 12-JAN-2005 | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | See response to DR comment 24 on p. 28 of CR#2 |
| | | | | 4 | N/A | * | As above. |
| | | | | 4 | Pending | | See P.7 and associated deficiency comment |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

[*] Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

**B. Other Supporting Documents:**

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |

**C. Related Documents:**

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|---|---|---|---|
| IND | 57,883 | Nycomed GmbH | |

## 18. CONSULTS/CMC-RELATED REVIEWS:

| CONSULTS | SUBJECT | DATE FORWARDED | STATUS/ REVIEWER | COMMENTS |
|---|---|---|---|---|
| Biometrics | N/A | | | See evaluation in P.8., pp.128 and 129 of CR#1, response to comment 25 in CR#2 on p. 28 of CR#2; and evaluation of P.8 in CR#4 |
| EES | PAI | 07 & 10-AUG-2009<br>02-SEP-2010 | ACCEPTABLE<br>Pending | OC decision of 27-AUG-2009<br>Two new sites added |
| Pharm/Tox | BYK20139 impurity allowed to (b) (4) in drug substance<br><br>Residual (b) (4) in drug substance | 03-AUG-2009<br><br>03-AUG-2009 | Final/Dr. Pei<br><br>Final/Dr. Pei | See attachment 1 of CR#1 for structure.<br><br>See p. 53 of CR#1; e-mail from Dr. Pei on 03-DEC-2009 indicates that BYK20139 is of no toxicological concern as it is also a drug metabolite.<br>See p. 68 of CR#1 |
| Biopharm | N/A | | | |
| LNC | N/A | | | |
| Methods Validation | N/A | | | Not deemed necessary, see p. 134 of CR#1; see p. 51 of CR#4 |
| OPDRA | | | | To be forwarded by PM to OSE |
| EA | N/A | | | Categorical exclusion granted, see p. 136 of CR#1 |
| Microbiology | N/A | | | Not needed at this time, see response to comment 25 on p. 28 of CR#2 |

# The Chemistry Review for NDA 22-522

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From the chemistry review perspective, the application is considered to be **approvable**. See the attached draft letter containing deficiency comments to be forwarded to the applicant by the Project Manager.

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

The applicant provides the following agreement (from the 22-JAN-2010, amendment):

"We herewith agree to revisit the drug substance particle size distribution (PSD) acceptance criteria after we 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."

## II. Summary of Chemistry Assessments

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

The drug product is Daxas® (roflumilast) Tablets and contain 500 mcg roflumilast/tablet. The solid oral dosage form is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The tablets are uncoated white to off-white round tablets embossed on one side with the letter "D" and on the other side with "500." The relatively small tablets have a diameter of 5 mm and weight of 66 mg. The trade packages consist of white, rectangular high-density polyethylene bottles with 30 or 90 tablets. There is also unit dose (b) (4) blisters with aluminum foil lidding for use in packaging trade or physician samples. There is a bulk package that is used for storage and shipping for final packaging. Currently the proposed expiration dating period for the drug product is 24 months, regardless of the package type. The stability data provided support this expiration dating period.

The formulation of the drug product does not contain any novel or non-compendial excipients and it is prepared for tablet compression (b) (4) No steps have been identified in the manufacturing process that are considered critical in terms of batch

reproducibility and product performance, although, as indicated below, roflumilast particle size is important to the attainment of the desired release rate as determined by dissolution testing. The Formula B tablet is that to-be-marketed and was used in the phase 3 trials.

The drug substance is roflumilast (USAN), a phosphodiesterase 4 inhibitor, and it has a (b) (4) retest period, which is acceptable based on the stability data provided in the application. The drug substance is micronized due to its poor water solubility. It has been found in only a single crystalline form (single polymorphic form) and it is characterized as BCS class 2 (poorly soluble, highly permeable) by the applicant. The particle size distribution of the roflumilast is observed to directly correlate with the dissolution or drug release from the dosage form. The drug substance by itself, and when formulated in the drug product, is observed to have superior chemical and physical stability.

### B. Description of How the Drug Product is Intended to be Used

The 500 mcg tablets are intended for once a day dosing in adults diagnosed with COPD. There are no special storage conditions necessary for the drug product and it is labeled for room temperature storage. A **24 month** expiration dating period is acceptable for the drug product.

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

The applicant will need to address the deficiency comments included in the attached draft letter on p. 53.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

CBertha/ONDQA/Reviewer/09/13/10
PPeri/ONDQA/DIV III/Acting Branch Chief_____

### C. CC Block

CHill/DPARP/Regulatory PM
PPeri/ONDQA/DIV III/Branch VIII/Acting Branch Chief
ASchroeder/DIV III/Branch VIII/Acting PAL
XHan Sarro/DPARP/Medical Officer
PJi/OCP/Clinical Pharmacologist
MWood/DPARP/Pharmacologist

51 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

| 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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CRAIG M BERTHA
09/13/2010

PRASAD PERI
09/14/2010
I concur

May 13, 2010

This CMC secondary review is superseded by the Division Director Memo checked in as a REV-QUALITY-03 (General Review) on May 10, 2010 by Christine Moore, the Acting Director.

For NMEs, the ONDQA policy is for the Division Director to include a DD Memo and check it into DARRTS in place of the CMC secondary review.

# Daxas (Roflumilast) Tablets

## NDA 22-522

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

**Applicant:** Forest Research Institute, Inc.
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

**Representative:** Lisa Travis, MS, RAC, Director Regulatory Affairs
Phone: 201 386 2031

**Indication:** DAXAS is an anti-inflammatory agent indicated for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

**Presentations:**
DAXAS is supplied as 500 mcg yellow, D-shaped yellow film coated tablets, embossed with "D" on one side. DAXAS tablets are available in HDPE bottles with child resistant closure containing 30 tablets or 90 tablets. (b) (4).

**EER Status:** Acceptable 27-Aug-2009

**Consults:** EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.
Pharmacology/Toxicology –Acceptable (Chem. Review 1)

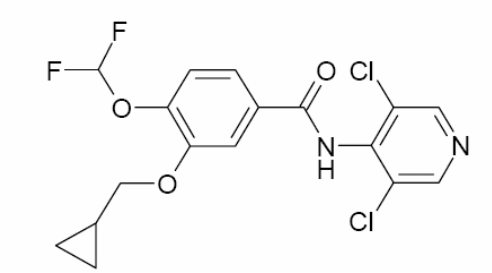
**Original Submission:** 15-JUL-2009

**Post-Approval CMC Commitments:**

The applicant agrees to revisit the drug substance PSD acceptance criteria after preparing multiple (e.g., 10) commercial batches.

**Drug Substance:**
The drug substance roflumilast is described as a white to off-white powder with the following IUPAC name: 3-(Cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22. It is an anti-inflammatory agent and a selective phosphodiesterase 4 (PDE4) inhibitor. The drug substance is micronized to a defined particle size distribution for formulation, due to the relatively low water solubility (0.52-0.56 mg/L at 21-22°C). The compound is practically insoluble in water and hexane, sparingly soluble in ethanol and freely soluble in acetone. The

use of (b) (4) enhances the solubility of the drug substance in water. The pH of the saturated solution in water is 6.35.



The drug substance is manufactured at two sites: Nycomed GmbH, Germany and (b) (4) The drug substance is micronized at (b) (4).

The drug substance is controlled by testing for Identity (IR, HPLC), Related Substances, Residual Solvents, Water Content, Sulfated Ash, Heavy Metals, and Assay (Content). A retest period of (b) (4) has been established for the drug substance.

**Conclusion:** The drug substance is satisfactory.

**Drug Product:**
Daxas® (roflumilast) tablets are D-shaped, yellow, film coated, containing 500 mcg each and are embossed on one side with the letter "D." Each film-coated tablet of DAXAS for oral administration contains the following inactive ingredients: lactose monohydrate, corn starch, (b) (4) and magnesium stearate (b) (4). The trade packages consist of a single high-density polyethylene bottle with a child-resistant closure that contains either 30 or 90 tablets. There are also physician samples that use (b) (4) blisters with aluminum foil lidding as packaging.

The drug product is manufactured, packaged, released, and stability tested at Nycomed GmbH, Germany. The drug product is also packaged at (b) (4).

The formulation is prepared for tablet compression (b) (4) No steps have been identified in the manufacturing process that are considered critical in terms of batch reproducibility and product performance, although, roflumilast particle size is important to the attainment of the desired release rate as determined by dissolution testing.

(b) (4)

The drug product is controlled by testing for Appearance, (b) (4), Identity (UV, HPLC), Identity of (b) (4), Purity (HPLC), Microbial Limits, Content Uniformity (HPLC or UV), and Dissolution.

The stability data provided support a 24 month expiration dating period for the bottled and blister packaged drug product.

**Outstanding issues: None**

**Conclusion:** The drug product is recommended for approval.

**Additional Items:**
All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for approval. Updated labeling needs to be provided by the applicant but a representative copy of the proposed carton is shown below.

| 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/

PRASAD PERI
03/31/2010

# Daxas (Roflumilast) Tablets
## NDA 22-522

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

**Applicant:** Forest Research Institute, Inc.
(originally filed under Nycomed, Inc.)
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

**Indication:** DAXAS is an anti-inflammatory agent indicated for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

**Presentations:** DAXAS is supplied as 500 mcg yellow, D-shaped yellow film coated tablets, embossed with "D" on one side. DAXAS tablets are available in HDPE bottles with child resistant closure containing 30 tablets or 90 tablets. (b) (4)

**EER Status:** Acceptable 27-Aug-2009

**Consults:** EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.
Pharmacology/Toxicology –Acceptable (L. Pei)

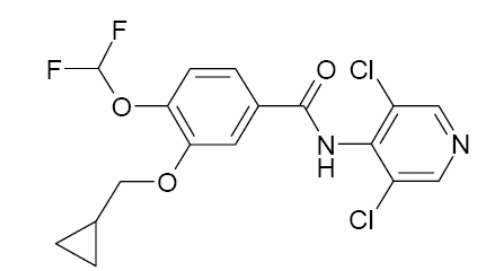
**Original Submission:** 15-JUL-2009

**Post-Approval CMC Commitments:**

The applicant agrees to revisit the drug substance PSD acceptance criteria after preparing multiple (e.g., 10) commercial batches.

**Drug Substance:**

The drug substance roflumilast is described as a white to off-white powder with the following IUPAC name: 3-(Cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22. It is an anti-inflammatory agent and a selective phosphodiesterase 4 (PDE4) inhibitor. The compound is practically insoluble in water and hexane, sparingly soluble in ethanol and freely soluble in acetone. The use of (b) (4) enhances the solubility of the drug substance in water. The pH of the saturated solution in water is 6.35. The drug substance is non-hygroscopic and a polymorph screen identified only a single polymorphic form.



The drug substance is manufactured at the following two sites: Nycomed GmbH, Germany and (b) (4). The drug substance is produced from a (b) (4). The manufacturing process description for the drug substance synthesis was described in the application and critical process steps and critical process parameters were identified. The drug substance is micronized to a defined particle size distribution for formulation, due to the relatively low water solubility (0.52-0.56 mg/L at 21-22°C). The drug substance micronization site is (b) (4).

Structural elucidation was provided by elemental analysis, UV, IR, NMR, Mass Spectroscopy and single crystal X-ray crystallography. The drug substance specification includes Identity (IR, HPLC), Related Substances (HPLC), Residual Solvents (headspace GC), Water Content (Karl Fischer), Sulfated Ash, Heavy Metals, Particle Size Distribution (laser diffraction), and Assay/Content (HPLC, titration). A retest period of (b) (4) has been established for the drug substance.

**Conclusion:** The drug substance is satisfactory.

**Drug Product:**

Daxas® (roflumilast) tablets are D-shaped, yellow, film coated, containing 500 mcg each and are embossed on one side with the letter "D." Each film-coated tablet of DAXAS for oral administration contains the following inactive ingredients: lactose monohydrate, corn starch, (b) (4) and magnesium stearate. (b) (4). All excipients are commonly used and of compendial grade (USP or NF).

The drug product is manufactured, packaged, released, and stability tested at Nycomed GmbH, Germany. The drug product is also packaged at (b) (4)

The formulation is prepared for tablet compression (b) (4). The tablets are film coated. No steps have been identified in the manufacturing process that are considered critical in terms of batch reproducibility and product performance, although, roflumilast particle size is important to the attainment of the desired release rate as determined by dissolution testing. A complete manufacturing process description was provided along with suitable in-process controls.

(b) (4)

(b) (4)

The drug product specifications include testing for Appearance, (b) (4), Identity (UV, HPLC), Identity of (b) (4), Purity (HPLC), Microbial Limits, Content Uniformity (HPLC or UV), and Dissolution. The stability data provided support a 24 month expiration dating period for the bottled and blister packaged drug product.

**Conclusion:** The drug product is recommended for approval.

**Additional Items:**

- All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

- The analytical methods used in the testing procedures (release, stability, and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for **approval.**

| 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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CHRISTINE M MOORE
05/10/2010

**CHEMISTRY REVIEW**

# NDA 22-522

## Daxas® (Roflumilast) Tablets

## Forest Research Institute, Inc.

**Craig M. Bertha, Ph.D.**
**Office of New Drug Quality Assessment/Division I/Branch II**
**for**
**Division of Pulmonary and Allergy Products**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 22-522

2. REVIEW #:3

3. REVIEW DATE: 25-JAN-2010

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Amendment | 04-DEC-2009 |
| Amendment | 02-DEC-2009 |
| Amendment | 11-SEP-2009 |
| Amendment | 24-AUG-2009 |
| Original | 15-JUL-2009 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment | 22-JAN-2010 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Forest Research Institute, Inc. |
| Address: | Harborside Financial Center, Plaza V<br>Jersey City, NJ 07311 |
| Representative: | Lisa L. Travis, MS, RAC<br>Director Regulatory Affairs |
| Telephone: | 201-386-2031 |

Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Daxas®
b) Non-Proprietary Name (USAN): roflumilast
c) Code Name/# (ONDC only): BYK20869, B9302-107, BY217
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: phosphodiesterase 4 (PDE4) inhibitor (for anti-inflammatory effect)

## 11. DOSAGE FORM: tablet (coated immediate release)

## 12. STRENGTH/POTENCY: 500 mcg/tablet

## 13. ROUTE OF ADMINISTRATION: oral

## 14. Rx/OTC DISPENSED: __X_Rx ___OTC

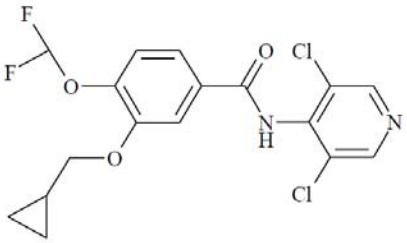
## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

The chemical name of Roflumilast is 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide (IUPAC); or N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide. Roflumilast is achiral and has CAS # 162401-32-3, the following structure, formula, and molecular weight:



| | |
|---|---|
| Molecular formula: | $C_{17}H_{14}Cl_2F_2N_2O_3$ |
| Relative molecular mass: | 403.22 |

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS[3] |
|---|---|---|---|---|---|---|---|
| (b) (4) | | | | 3 | Adequate | 18-SEP-2007 | |
| | | | | 3 | Adequate | 12-JAN-2005 | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | See response to DR comment 24 on p. 28 of CR#2 |
| | | | | 4 | N/A | * | As above. |

Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

[*] Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

**B. Other Supporting Documents:**

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |

**C. Related Documents:**

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|---|---|---|---|
| IND | 57,883 | Nycomed GmbH | |

## 18. CONSULTS/CMC-RELATED REVIEWS:

| CONSULTS | SUBJECT | DATE FORWARDED | STATUS/ REVIEWER | COMMENTS |
|---|---|---|---|---|
| Biometrics | N/A | | | See evaluation in P.8., pp.128 and 129 of CR#1, and response to comment 25 in CR#2 on p. 28 of CR#2 |
| EES | PAI | 07 & 10-AUG-2009 | ACCEPTABLE | OC decision of 27-AUG-2009 |
| Pharm/Tox | BYK20139 impurity allowed to (b) (4) in drug substance | 03-AUG-2009 | Final/Dr. Pei | See attachment 1 of CR#1 for structure.<br><br>See p. 53 of CR#1; e-mail from Dr. Pei on 03-DEC-2009 indicates that BYK20139 is of no toxicological concern as it is also a drug metabolite. |
| | Residual (b) (4) in drug substance | 03-AUG-2009 | Final/Dr. Pei | See p. 68 of CR#1 |
| Biopharm | N/A | | | |
| LNC | N/A | | | |
| Methods Validation | N/A | | | Not deemed necessary, see p. 134 of CR#1 |
| OPDRA | | | | To be forwarded by PM to OSE |
| EA | N/A | | | Categorical exclusion granted, see p. 136 of CR#1 |
| Microbiology | N/A | | | Not needed at this time, see response to comment 25 on p. 28 of CR#2 |

# The Chemistry Review for NDA 22-522

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From the chemistry review perspective, the application is recommended to be **approved.**

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

The applicant provides the following agreement (from the 22-JAN-2010, amendment):

"We herewith agree to revisit the drug substance particle size distribution (PSD) acceptance criteria after we 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."

## II. Summary of Chemistry Assessments

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

The drug product is Daxas® (roflumilast) Tablets and the strength is 500 mcg/tablet. The solid oral dosage form is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The tablets are yellow, film-coated, "D-shaped," and are embossed on one side with the letter "D." The trade packages consist of a single high-density polyethylene bottle with a child-resistant closure that contains either 30 or 90 tablets. There are also physician samples that use (b) (4) blisters with aluminum foil lidding as packaging. Currently the proposed expiration dating period for the drug product in both package types is 24 months. The updated stability data provided support this expiration dating period for the bottled and blister packaged drug product.

The formulation of the drug product does not contain any novel or non-compendial excipients and it is prepared for tablet compression (b) (4) No steps have been identified in the manufacturing process that are considered critical in terms of batch reproducibility and product performance, although, as indicated below, roflumilast particle size is important to the attainment of the desired release rate

as determined by dissolution testing. (b) (4)

The drug substance is roflumilast (USAN), a phosphodiesterase 4 inhibitor, and it has a (b) (4) retest period, which is acceptable based on the stability data provided in the application. The drug substance is micronized due to its poor water solubility. It has been found in only a single crystalline form (single polymorphic form) and it is characterized as BCS class 2 (poorly soluble, highly permeable) by the applicant. The particle size distribution of the roflumilast is observed to directly correlate with the dissolution or drug release from the dosage form. The drug substance by itself, and when formulated in the drug product, is observed to have superior chemical and physical stability.

### B. Description of How the Drug Product is Intended to be Used

The 500 mcg tablets are intended for once a day dosing in adults diagnosed with COPD. There are no special storage conditions necessary for the drug product and it is labeled for room temperature storage. A **24 month** expiration dating period is acceptable for the drug product in the bottles and in the blister packaging for physician samples.

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

N/A

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

CBertha/ONDQA/Reviewer/01/25/10
PPeri/ONDQA/DIV I/Acting Branch Chief_____

### C. CC Block

CHill/DPAP/Regulatory PM
PPeri/ONDQA/DIV I/Branch II/Acting Branch Chief
ASchroeder/DIV I/Branch II/Acting PAL
XHan Sarro/DPAP/Medical Officer
JPing/OCP/Clinical Pharmacologist
LPei/DPAP/Pharmacologist

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| 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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CRAIG M BERTHA
01/25/2010

PRASAD PERI
01/25/2010
I Concur

**CHEMISTRY REVIEW**

# NDA 22-522

## Daxas® (Roflumilast) Tablets

## Nycomed GmbH

**Craig M. Bertha, Ph.D.**
**Office of New Drug Quality Assessment/Division I/Branch II**
**for**
**Division of Pulmonary and Allergy Products**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 22-522

2. REVIEW #:2

3. REVIEW DATE: 10-DEC-2009

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Amendment | 24-AUG-2009 (change of US contact) |
| Original | 15-JUL-2009 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment | 04-DEC-2009 |
| Amendment | 02-DEC-2009 |
| Amendment | 11-SEP-2009 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Forest Research Institute, Inc. |
| Address: | Harborside Financial Center, Plaza V<br>Jersey City, NJ 07311 |
| Representative: | Lisa L. Travis, MS, RAC<br>Director Regulatory Affairs |
| Telephone: | 201-386-2031 |

Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Daxas®
b) Non-Proprietary Name (USAN): roflumilast
c) Code Name/# (ONDC only): BYK20869, B9302-107, BY217
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: phosphodiesterase 4 (PDE4) inhibitor (for anti-inflammatory effect)

## 11. DOSAGE FORM: tablet (coated immediate release)

## 12. STRENGTH/POTENCY: 500 mcg/tablet

## 13. ROUTE OF ADMINISTRATION: oral

## 14. Rx/OTC DISPENSED: __X_Rx ___OTC

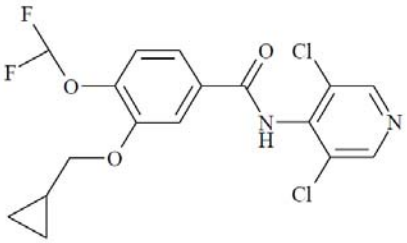
## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

The chemical name of Roflumilast is 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide (IUPAC); or N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide. Roflumilast is achiral and has CAS # 162401-32-3, the following structure, formula, and molecular weight:



| | |
|---|---|
| Molecular formula: | $C_{17}H_{14}Cl_2F_2N_2O_3$ |
| Relative molecular mass: | 403.22 |

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED (b) (4) | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS[3] |
|---|---|---|---|---|---|---|---|
| | | | | 3 | Adequate | 18-SEP-2007 | |
| | | | | 3 | Adequate | 12-JAN-2005 | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | |
| | | | | 4 | N/A | * | See response to DR comment 24 on page 28 |
| | | | | 4 | N/A | * | As above. |

Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

[*] Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

**B. Other Supporting Documents:**

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |

**C. Related Documents:**

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|---|---|---|---|
| IND | 57,883 | Nycomed GmbH | |

## 18. CONSULTS/CMC-RELATED REVIEWS:

| CONSULTS | SUBJECT | DATE FORWARDED | STATUS/ REVIEWER | COMMENTS |
|---|---|---|---|---|
| Biometrics | N/A | | | See evaluation in P.8., pp.128 and 129 of CR#1, and response to comment 25 in CR#2 on p. 28 |
| EES | PAI | 07 & 10-AUG-2009 | ACCEPTABLE | OC decision of 27-AUG-2009 |
| Pharm/Tox | BYK20139 impurity allowed to (b) (4) in drug substance | 03-AUG-2009 | Final/Dr. Pei | See attachment 1 of CR#1 for structure.<br>See p. 53 of CR#1; e-mail from Dr. Pei on 03-DEC-2009 indicates that BYK20139 is of no toxicological concern as it is also a drug metabolite. |
| | Residual (b) (4) in drug substance | 03-AUG-2009 | Final/Dr. Pei | See p. 68 of CR#1 |
| Biopharm | N/A | | | |
| LNC | N/A | | | |
| Methods Validation | N/A | | | Not deemed necessary, see p. 134 of CR#1 |
| OPDRA | | | | To be forwarded by PM to OSE |
| EA | N/A | | | Categorical exclusion granted, see p. 136 of CR#1 |
| Microbiology | N/A | | | Not needed at this time, see response to comment 25 on p. 28 |

# The Chemistry Review for NDA 22-522

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From the chemistry review perspective, the application is considered to be **approvable** pending the resolution of the deficiencies outlined in the attached draft letter. It is requested that the PM send the comments in the attached draft information request letter to the applicant as soon as feasible.

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

The applicant will be asked to agree to revisit and revise, if warranted based on commercial batch data, the acceptance criteria for the particle size distribution for the drug substance (see comment 4 in the attached draft letter).

## II. Summary of Chemistry Assessments

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

The drug product is Daxas® (roflumilast) Tablets and the strength is 500 mcg/tablet. The solid oral dosage form is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The tablets are yellow, film-coated, "D-shaped," and are embossed on one side with the letter "D." The trade packages consist of a single high-density polyethylene bottle with a child-resistant closure that contains either 30 or 90 tablets. There are also physician samples that use (b) (4) blisters with aluminum foil lidding as packaging. Currently the proposed expiration dating period for the drug product in both package types is 24 months. The updated stability data provided support this expiration dating period for the bottled and blister packaged drug product.

The formulation of the drug product does not contain any novel or non-compendial excipients and it is prepared for tablet compression (b) (4) No steps have been identified in the manufacturing process that are considered critical in terms of batch reproducibility and product performance, although, as indicated below, roflumilast particle size is important to the attainment of the desired release rate as determined by dissolution testing. (b) (4)

(b) (4)

The drug substance is roflumilast (USAN), a phosphodiesterase 4 inhibitor, and has a (b) (4) retest period, which is acceptable based on the stability data provided in the application. The drug substance is micronized due to its poor water solubility. It has been found in only a single crystalline form (single polymorphic form) and it is characterized as BCS class 2 (poorly soluble, highly permeable) by the applicant. The particle size distribution of the roflumilast is observed to directly correlate with the dissolution or drug release from the dosage form. The drug substance, and the drug substance when formulated in the drug product, is observed to have superior chemical and physical stability.

### B. Description of How the Drug Product is Intended to be Used

The 500 mcg tablets are intended for once a day dosing in adults diagnosed with COPD. There are no special storage conditions necessary for the drug product and it is labeled for room temperature storage. A **24 month** expiration dating period is acceptable for the drug product in the bottles and in the blister packaging for physician samples.

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

The application is considered to be approvable but there are several items that still need to be addressed before approval can be recommended from the CMC perspective. The application is still inconsistent with regard to the designation of the starting material for the synthesis. The system suitability requirements for the drug substance impurity methods are still deficient and need revision to meet the standards expected by the Agency. The application is inconsistent with respect to the dissolution acceptance criteria that will be applied at release and during stability testing.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

CBertha/ONDQA/Reviewer/12/10/09
PPeri/ONDQA/DIV I/Acting Branch Chief_____

### C. CC Block

CHill/DPAP/Regulatory PM

LJafari/DPAP/SPM
PPeri/ONDQA/DIV I/Branch II/Acting Branch Chief
ASchroeder/DIV I/Branch II/Acting PAL
XHan Sarro/DPAP/Medical Officer
JPing/OCP/Clinical Pharmacologist
LPei/DPAP/Pharmacologist

28 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22522 | GI-1 | NYCOMED GMBH | DAXAS(ROFLUMILAST 500 MCG TABLETS |
| NDA-22522 | ORIG-1 | NYCOMED GMBH | DAXAS(ROFLUMILAST 500 MCG 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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CRAIG M BERTHA
12/10/2009

PRASAD PERI
12/10/2009
I concur

**CHEMISTRY REVIEW**

# NDA 22-522

## Daxas® (Roflumilast) Tablets

## Nycomed GmbH

**Craig M. Bertha, Ph.D.**
**Division of Pulmonary and Allergy Products**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 22-522

2. REVIEW #:1

3. REVIEW DATE: 25-AUG-2009

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment | 24-AUG-2009 (change of US contact) |
| Original | 15-JUL-2009 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Nycomed GmbH |
| Address: | Byk-Gulden-Str. 2<br>78467 Konstanz<br>Germany |
| Representative: | Dr. Christoph Bunte |
| Telephone: | +49 7531-84-4236 |
| US Contact Name: | PPD Development, LP |
| Address: | 1400 Perimeter Parkway<br>Morrisville, NC<br>27560-7200 |

Chemistry Review Data Sheet

Representative: Kevin B. Johnson, Ph.D., MBA, Assoc. Dir., US Reg. Affairs

Telephone: 919-456-4442

## 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Daxas®
b) Non-Proprietary Name (USAN): roflumilast
c) Code Name/# (ONDC only): BYK20869, B9302-107, BY217
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: phosphodiesterase 4 (PDE4) inhibitor (for anti-inflammatory effect)

## 11. DOSAGE FORM: tablet (coated immediate release)

## 12. STRENGTH/POTENCY: 500 mcg/tablet

## 13. ROUTE OF ADMINISTRATION: oral

## 14. Rx/OTC DISPENSED: __X_Rx ___OTC

## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

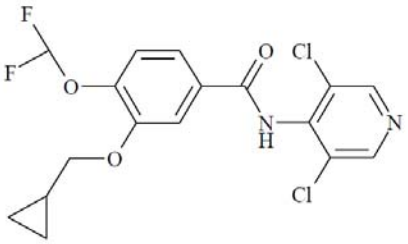
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

The chemical name of Roflumilast is 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide (IUPAC); N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-

difluoromethoxybenzamide. Roflumilast is achiral and has CAS # 162401-32-3, the following structure, formula, and molecular weight:



| | |
|---|---|
| Molecular formula: | $C_{17}H_{14}Cl_2F_2N_2O_3$ |
| Relative molecular mass: | 403.22 |

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS[3] |
|---|---|---|---|---|---|---|---|
| (b) (4) | | | | 3 | Adequate | 18-SEP-2007 | |
| | | | | 3 | Adequate | 12-JAN-2005 | |
| | | | | | 4 | * | |
| | | | | | 4 | * | |
| | | | | | 4 | * | |
| | | | | | 4 | * | |
| | | | | | 4 | * | |
| | | | | | 4 | * | |
| | | | | | 4 | * | |
| | | | | | 4 | * | |
| | | | | | 4 | * | |
| | | | | | Not reviewed | | Information will be sought from applicant, see deficiency on p. 119 |
| | | | | | Not reviewed | | As above. |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

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

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

[*] Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

**B. Other Supporting Documents:**

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |

**C. Related Documents:**

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|---|---|---|---|
| IND | 57,883 | Nycomed GmbH | |
| | | | |

## 18. CONSULTS/CMC-RELATED REVIEWS:

| CONSULTS | SUBJECT | DATE FORWARDED | STATUS/ REVIEWER | COMMENTS |
|---|---|---|---|---|
| Biometrics | N/A | | | See evaluation in P.8., pp. 128, 129 |
| EES | PAI | 07 & 10-AUG-2009 | Pending | |
| Pharm/Tox | BYK20139 impurity allowed to (b) (4) in drug substance<br>Residual (b) (4) in drug substance | 03-AUG-2009<br>03-AUG-2009 | Pending/Dr. Pei<br>Final/Dr. Pei | See attachment 1 for structure.<br>See p. 53<br>See p. 68 |
| Biopharm | N/A | | | |
| LNC | N/A | | | |
| Methods Validation | N/A | | | Not deemed necessary, see p. 134. |
| OPDRA | | | | To be forwarded by PM to OSE |
| EA | N/A | | | Categorical exclusion granted, see p. 136 |
| Microbiology | N/A | | | Not needed at this time, see deficiency on p. 129 |

# The Chemistry Review for NDA 22-522

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From the chemistry review perspective, the application is considered to be **approvable** pending the resolution of the deficiencies outlined in the attached draft letter. Also, the recommendation from the Office of Compliance for the pre-approval inspection is pending.

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

None at this time.

## II. Summary of Chemistry Assessments

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

The drug product is Daxas® (roflumilast) Tablets and the strength is 500 mcg/tablet. The solid oral dosage form is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The tablets are yellow, film-coated, "D-shaped," and are embossed on one side with the letter "D." The trade packages consist of a single high-density polyethylene bottle with a child-resistant closure that contains either 30 or 90 tablets. There are also physician samples that use (b) (4) blisters with aluminum foil lidding as packaging. Currently the proposed expiration dating period for the drug product in both package types is 24 months. With the exception of microbiological purity, for which no data are provided, the stability data provided in the original application support this expiration dating period.

The formulation of the drug product does not contain any novel or non-compendial excipients and it is prepared for tablet compression (b) (4) . No steps have been identified in the manufacturing process that are considered critical in terms of batch reproducibility and product performance, although, as indicated below, roflumilast particle size is important to the attainment of the desired release rate as determined by dissolution testing. A key point to note is that the formulation that was used in the phase III trials differs from that to be marketed even though the manufacturing processes for both are highly similar. (b) (4)

(b) (4)

The drug substance is roflumilast (USAN), a phosphodiesterase 4 inhibitor, and has a (b) (4) retest period which is acceptable based on the stability data provided in the application. The drug substance is micronized due to its poor water solubility. It has been found in only a single crystalline form (single polymorphic form) and it is characterized as BCS class 2 (poorly soluble, highly permeable) by the applicant. The particle size distribution of the roflumilast is observed to directly correlate with the dissolution or drug release from the dosage form. The applicant will be asked to justify the current, and apparently wide, acceptance criteria for the particle size distribution parameters. The drug substance, and the drug substance when formulated in the drug product, is observed to have superior chemical and physical stability.

**B. Description of How the Drug Product is Intended to be Used**

The 500 mcg tablets are intended for once a day dosing in adults diagnosed with COPD. There are no special storage conditions necessary for the drug product and it is labeled for room temperature storage.

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

Deficiency comments are captured in the draft letter on p. 137 of this review. Both the methods for testing of the drug substance and the drug product are in need of revision as they do not include sufficient detail or system suitability criteria to be considered suitable for regulatory purposes. The particle size distribution (PSD) acceptance criteria for the drug substance are broad relative to the data presented for the parameters that define the PSD. The PSD directly impacts the drug product release from the dosage forms, as determined by dissolution testing, thus the applicant either needs to tighten the PSD acceptance criteria to reflect the typical data that have been collected or will need to provide dissolution data that can justify wider PSD acceptance criteria. Based on the dissolution data provided for the drug product both at release and on stability, the applicant should tighten the criteria to assure (b) (4) time-point. Additional information is necessary with regard to the controls for the blister packaging foil lidding. Microbiological data are needed for stability samples in order to assess the proposed expiration dating period for the drug product as packaged in both the bottles and blisters. Stability data should be provided to support the use of the bulk packaging for shipment of the drug product to the proposed repackager, otherwise the applicant will be asked to withdraw the repackaging site from the application. Other deficiencies and comments requesting clarification are included in the draft letter.

# III. Administrative

## A. Reviewer's Signature

## B. Endorsement Block

CBertha/ONDQA/Reviewer/8/25/09
AAl-Hakim/ONDQA/DIV I/Branch Chief_____

## C. CC Block

CHill/DPAP/Regulatory PM
LJafari/DPAP/SPM
PPeri/ONDQA/DIV I/Branch II/PAL
XHan Sarro/DPAP/Medical Officer
JPing/OCP/Clinical Pharmacologist
LPei/DPAP/Pharmacologist

132 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---|---|---|---|
| NDA 22522 | ORIG 1 | NYCOMED GMBH | DAXAS(ROFLUMILAST 500 MCG TABLETS |
| NDA 22522 | ORIG 1 | NYCOMED GMBH | DAXAS(ROFLUMILAST 500 MCG 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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CRAIG M BERTHA
08/25/2009

ALI H AL HAKIM
08/28/2009