MEMORANDUM
May 10, 2000

TO: John K. Jenkins, M.D.
Leah Ripper
FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 20-831 (Formoterol fumarate inhalation powder)

I have reviewed the information to support the approvability of this NDA and concur with the recommendations of the Pharmacology/Toxicology Reviewers. The carcinogenicity, mutagenicity, impairment of fertility, and pregnancy category sections of the physician labelling, as written by the sponsor, are unacceptable. These sections should be re-written to conform with the label content suggested by Dr. Luqi Pei (contained in the review, stamp dated April 25, 2000, of subsequent submissions dated 10/19/98 and 11/23/99). Specifically, carcinogenicity study systemic exposure comparisons, as written by Dr. Pei, more accurately reflect the data and current practice in CDER concerning writing style. In addition, Dr. Pei includes information on the actual mutagenicity/genotoxicity studies that were conducted, as well as specific effects observed in nonclinical reproductive toxicity studies. These details are essential for the label to be considered accurate.

/S/

Kenneth L. Hastings, Dr.P.H.
Acting Associate Director for Pharmacology/Toxicology

ADDENDUM
Feb. 13, 2001

Although a final version of the product label was not available, changes to the draft label appear to have been made that would correct the problems originally noted for the pharmacology/toxicology sections.

/s/

Kenneth Hastings
2/13/01 09:40:39 AM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL

Memorandum

To: NDA 20-831
From: Robin A. Huff, Ph.D., Pharmacology Team Leader /S/ 4-26-00
Date: April 26, 2000
Re: Team Leader NDA Summary

Overall Pharmacology/Toxicology Recommendation - Approvable

APR 27 2000

Background

NDA 20-831 is for formoterol fumarate (Foradil™ Aerolizer, dry powder inhaler), a long-acting beta-agonist. Formoterol is a new molecular entity, intended for the treatment of asthma and bronchoconstriction in patients —years of age and older with reversible obstructive airways disease. This application was deemed approvable in June 1998; however, a labeling review was not conducted at that time in light of unresolved CMC issues that were paramount for approval. Preclinical labeling comments have now been prepared (see Dr. Pei's April 25, 2000 review). The preclinical development of this application has already been summarized in Dr. Hilary Sheevers' memo dated June 1, 1998; however, finalization of the Executive Carcinogenicity Assessment Committee's findings remained an open issue.

Resolution of Carcinogenicity Assessment Committee Issues

Four carcinogenicity studies were conducted for the NDA, drinking water and dietary studies in both mice and rats. These studies were originally taken to the ECAC on April 14, 1998, but the Committee was unable to render a final assessment due to lack of information. After the requested information was provided by the sponsor and reviewed (see Dr. Pei's March 13, 2000 review), the studies were presented at the April 11, 2000 meeting of the ECAC, an accounting of which can be found in the meeting minutes. The ECAC recommended including the following tumor types in the label, but as detailed below, the occurrence of these tumors does not adversely affect approval of formoterol.

1. The incidence of leiomyomas of the female genital tract was increased in both rat studies and the dietary mouse study (leiomyomas were not reported in the mouse drinking water study which used B6C3F1 mice, a strain reported to be resistant to beta agonist effects on the uterus; Gibson *et al*, 1987). The NOAEL in the rat studies provides a safety margin of 225 fold based on AUC exposure. Although a NOAEL was not established in the mouse dietary study, other beta agonist drugs have also been shown to produce leiomyomas, and development of this tumor type has been characterized as a pharmacodynamic response that can be blocked by coadministration of a beta antagonist (Gibson *et al*, 1987). Whereas beta-2 receptors predominate in the rodent uterus, they are not extensively expressed in human uterus (Cheng and Woodward, 1984; Berg-Johnsen and Nesheim, 1976; Lossius and Nesheim, 1976; Lehrer, 1965), suggesting diminished potential for

development of leiomyomas in humans. In 1981, the Pulmonary-Allergy Drugs Advisory Committee determined that the benefit-risk analysis for beta agonists was not sufficiently affected by the development of leiomyomas in rodents to withhold approval.

2. The incidence of ovarian theca cell tumors was increased at all doses in the rat dietary study. It is possible to postulate a pharmacodynamic mechanism involving increased cellular cAMP in steroid-producing cells leading to steroidogenesis and stimulation of ovarian theca cells. However, these tumors did not occur in the rat drinking water study, which used doses up to three times greater than doses in the dietary study, nor they did not occur in either of the mouse studies. Furthermore, the tumors in the rat dietary study were benign.

3. The incidence of adrenal subcapsular adenomas and carcinomas was increased at all doses in the mouse drinking water study. However, these tumors were not seen at the lower doses used in the dietary study, providing a safety margin of 300 fold based on AUC exposure.

4. The incidence of hepatocarcinoma was increased in the mouse dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males. The NOAEL of 5 mg/kg provides a safety margin of 30 fold based on AUC exposure).

Rationale for Animal to Human Dose Comparisons in the Labeling

Sufficient toxicokinetic data were not available to make exposure estimates for the oral gavage reproductive toxicology studies; therefore, dose comparisons in the corresponding sections of labeling were made on a mg/m^2 basis. By contrast, toxicokinetic data collected in the dietary carcinogenicity studies allowed exposure to be estimated and compared to human exposure. In the carcinogenicity section, when dose comparisons are made on a mg/m^2 basis it is customary to make comparisons to both adult and pediatric doses. However, since in this case exposure data is available for adults and results in a more conservative comparison than body surface area calculations for either adults or children, a single comparison to "human exposure at the maximum recommended daily dose" has been made for each tumor finding.

APPEARS THIS WAY
ON ORIGINAL

Memorandum

To: NDA [redacted] 20-831
From: Hilary V. Sheevers - Pharm./Tox. Team Leader 6/15/98
Re: Team Leader NDA Summary, HFD 570
Date: June 1, 1998

Overall Recommendation (Pharm/Tox): Approvable

Foradil is the oral inhalation formulation of the beta agonist formoterol fumorate intended for asthmatics ages — years and above; the proposed dosage is up to — mcg/day in adults. As a new molecular entity, a large number of preclinical studies were performed, including 4 carcinogenicity studies, and a complete battery of reprotoxicity, genotoxicity, and chronic toxicity studies.

Outstanding Issues:

The primary outstanding issue is associated with the sponsor's assay for drug plasma levels. The sponsor stated throughout their pharm/tox submission that they had "problems" with the assay, and the final values given (particularly for the rat carcinogenicity studies) are far above what would be expected given the doses, internally inconsistent, and not consistent with values reported in another sponsor's submission for formoterol. The sponsor has attempted to clarify the data, but their attempts have been inadequate. As a result of this missing data, the report from the Executive CAC remains outstanding, and will not be completed until the AUC information is clarified.

A secondary issue, again related to the carcinogenicity studies, is that the reports of tumor numbers are not consistent among tables submitted by the sponsor. The sponsor has been asked to clarify the number of tumor findings.

The suggested labeling will be finalized upon submission of the above information.

Summary of Significant Preclinical Studies:

A large set of preclinical studies were performed for Formoterol. In short-term and chronic toxicity studies in rats and dogs, cardiotoxicity appeared as the major toxicity of concern. This was manifested in dogs as increased heart rate and force, reddening in the mouth, and myocardial

degeneration in dogs at doses of 3 mcg/kg/day and above (approximately 6 times the adult dose based on body surface area comparisons). Increased heart weight (30 mcg/kg) and myocardial fibrosis (400 mcg/kg) was also noted in rats after 6-months of treatment. Other toxicities noted were related to exaggerated pharmacodynamic effects of beta agonists.

Reproduction studies were performed in the rat to test impairment of fertility (Segment I) and multi-generational reproductive effects (Segment III), and in rats and rabbits to test for teratogenicity (Segment II). Oral formoterol did not impair fertility in males or females up to doses that resulted in toxicity (body weight, organ weight changes). Teratology studies were performed with oral formulations. In rats, slight delayed ossification was observed in all treated groups; fetotoxicity and heart weights were increased at 6 mg/kg and above. In rabbits, a decrease in neonatal survival was noted at 500/mg/kg. In the peri- and post-natal study in rats, decreased body weight and increased death (stillbirth, neonatal death) was noted in treated groups.

Four carcinogenicity studies were performed: two dietary studies and two drinking water studies. The sponsor was permitted to bridge these studies with chronic inhalation studies. Noted tumors include ovarian leiomyomas at doses 6 or more times greater than the human dose. This tumor type is an expected finding in most rodents treated with beta agonists. In mice, a hepatocellular carcinoma and adrenal adenoma and carcinoma was noted at 60-800 times the adult dose. Bridging inhalation studies revealed no preneoplastic findings in the lung. All genotoxicity and mutagenicity studies were negative for formoterol.

CC: Division file, Jani, Zoetis

E L E C T R O N I C M A I L M E S S A G E

Date: 22-Jun-1998 11:20am EDT
From: Leah Ripper
RIPPER
Dept: HFD-102 PKLN 13B28
Tel No: 301-827-5920 FAX 301-480-6644

TO: Parinda Jani (JANIP)

Subject: Foradil

Here are Joe DeGeorge's comments, dated 6/19/98, he says he already talked to the reviewer about them:

1. In the letter, deficiency #41 is not clear and has errors in the units presented. As it exists, it is not interpretable, i.e., the "units" for AUC as given are "concentration" not "AUC".

2. Suggest that "scientific notation" (i.e., 10(superscript)x) not be used in comparison in label and that approxiate factors be used (i.e., 80 fold and 3000 fold) rather than 0.8 x 10(superscript)2 and 32.4 x 10(superscript)2.

Complete comments on label will await final verison with approval.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-831

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936

MAY 24 2000

Attention: Kathleen Creedon, Ph.D.
Assistant Director
Drug Regulatory Affairs

Dear Dr. Creedon:

Please refer to your new drug application (NDA) dated June 24, 1997, received June 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil Aerolizer (formoterol fumarate inhalation powder).

We acknowledge receipt of your submissions dated June 1, October 19, November 10, and December 10, 1998, November 23, 1999, and February 2 and 16, and March 30, 2000. Your submission of November 23, 1999, constituted a complete response to our June 26, 1998, action letter.

We also refer to your submission dated April 28, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies.

9. Submit a financial certification or disclosure statement for pediatric study 049 per the requirements of 21 CFR 314.50(k).

10. The following are preliminary comments on the labeling. Revise the draft package insert and carton and container labels to reflect the revisions listed below. Further labeling comments will be provided once the deficiencies noted in this letter are adequately addressed.

a. The naming and labeling of the product do not provide sufficient clarity on the name of the device versus the name of the product. Revise the proposed name and labeling to clearly distinguish the drug product (i.e., the formoterol inhalation powder in capsules) from the delivery device (i.e., Aerolizer).

b. Revise the DESCRIPTION section to describe the emitted dose delivered in vitro, along with the conditions of the in vitro testing. Also, describe typical flow-rates generated by patients through the device.

c. Revise the Mechanism of Action subsection of the CLINICAL PHARMACOLOGY section as follows:

> Formoterol fumarate is a long-acting selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist). Inhaled formoterol fumarate acts locally in the lung. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart, comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have effect on the cardiovascular system.
>
> The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

d. Revise the Absorption discussion under the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section as follows:

Following inhalation of a single 120-mcg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing.

Following inhalation of 12 to 96 mcg of formoterol fumarate by 10 healthy males, urinary excretion of both (R,R)- and (S,S)-enantiomers of formoterol increased proportionally to the dose. Thus, the absorption of formoterol following inhalation appears to be linear over the dose range studied.

In a study in asthmatic patients, when formoterol 12 or 24 mcg twice daily was given by oral inhalation to steady-state, the accumulation index ranged from 1.67 to 2.08 based on the urinary excretion of unchanged formoterol. This suggests some accumulation of formoterol in plasma during multiple dosing. The excreted amounts of formoterol at steady state were close to those predicted based on single-dose kinetics.

[ ]

e. Revise the Pharmacodynamics and Clinical Trials subsections of the CLINICAL PHARMACOLOGY section into separate discussions. The Pharmacodynamics subsection should contain important pharmacodynamic information from either specific PK/PD trials or from the clinical studies, particularly information related to systemic safety. Additionally, this section should include descriptions of trials done to examine tachyphylaxis and tolerance.

The Clinical Trials subsection should be substantially revised to achieve a more succinct and clear description of trial design and the resulting data. Only one set of graphs from the pivotal trials should be included. The narrative can make clear that the results of the two trials were similar. The discussion of the Pediatric Trial should be done with a narrative alone, without a graph. Again, this discussion should achieve a succinct description of the trial design, demographics, and outcome.

f. Revise the INDICATIONS AND USAGE section as follows:

[redacted]

Foradil is also indicated for the prevention of exercise-induced bronchospasm (EIB) in adults and children 12 years of age and older, administered on an as-needed basis. [redacted]

Foradil can be used concomitantly with short-acting beta$_2$-agonists, inhaled or systemic corticosteroids, and theophylline therapy (see PRECAUTIONS-Drug Interactions). [redacted], a satisfactory clinical response to Foradil does not eliminate the need for continued treatment with an anti-inflammatory agent.

g. Revise the WARNINGS section to be consistent with other long- and short-acting inhaled beta-agonist products.

h. Revise the General subsection of the PRECAUTIONS section to be consistent with other long- and short-acting inhaled beta-agonist products.

i. Revise the Information for Patients subsection of the PRECAUTIONS section as follows:

It is important that patients understand how to use the Aerolizer inhalation device appropriately and how it should be used in relation to other asthma medications they are taking. (Patient Instructions For Use.)

[redacted]

Foradil is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist. The physician should provide the patient with such medication and instruct the patient in how it should be used. Patients should be instructed to seek medical attention if their symptoms worsen, if Foradil treatment becomes less effective or if they need more inhalations of a short-acting beta$_2$-agonist than usual. Patients should not inhale more than the contents of the prescribed number of capsules at any one time. The daily dosage of Foradil should not exceed [redacted]

When Foradil is used for the prevention of EIB, the contents of one [redacted] should be taken at least 15 minutes prior to exercise. Additional doses of Foradil should not be used for 12 hours. [redacted]

Foradil should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with Foradil.

Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Patients should be informed never to use Foradil with a spacer and never to exhale into the Aerolizer device.

Patients should avoid exposing the Foradil capsules to moisture and should handle the capsules with dry hands. Aerolizer should never be washed, [redacted]

Women should be advised to contact their physician if they become pregnant or are nursing.

[redacted]

j. Revise the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section as follows:

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately ——— human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately ——— human exposure at the maximum recommended daily inhalation dose). This finding was not produced in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately ——— human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately ——— human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately ——— human exposure at the maximum recommended daily inhalation dose). Increases in leiomyomas of the female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts, and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 510 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis).

k. Revise the Pregnancy-Teratogenic Effects, Use in Labor and Delivery, and the Nursing Mothers subsections of the PRECAUTIONS section as follows:

Pregnancy/Teratogenic Effects PREGNANCY CATEGORY C: Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately —— times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately ——— the maximum recommended daily inhalation dose in humans on a mg/m^2 basis). When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight.

[ ]

Use in Labor and Delivery: Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately —— times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above in rats receiving the drug for several days at the end of pregnancy. These effects were not produced at a dose of 0.2 mg/kg (approximately ——— the maximum recommended daily inhalation dose in humans on a mg/m^2 basis). There are no adequate and well-controlled human studies that have investigated the effects of formoterol during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, formoterol should be used during labor only if the potential benefit justifies the potential risk —

Nursing Mothers: In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised when formoterol is administered to nursing women.

There are no well-controlled human studies of the use of formoterol in nursing mothers.

l. Revise the PRECAUTIONS-Geriatric Use subsection in accordance with the August 27, 1997, Federal Register Notice (62 FR 45313). This rule requires that all information on the safe and effective use of formoterol in elderly patients, i.e., patients 65 years of age and older, be included in the labeling. This subsection should include comments on limitations, hazards, and monitoring related to formoterol administration in this patient population. In addition, formoterol should be characterized by one of the following statements: 1) having insufficient data to determine if the effect is different in the elderly than in younger patients; 2) having sufficient data to make a determination about a different effect in the elderly and younger patients and no difference was found; or 3) having sufficient data to make a determination about a different effect in the elderly and younger patients and a difference was found.

Also, provide a breakdown of the number of patients 65 years of age and older who have received formoterol and how the response in this patient population compares to the response seen in younger patients, in terms of both safety and efficacy.

m. Revise the ADVERSE REACTIONS section as follows:

Adverse reactions to Foradil are similar in nature to other selective $beta_2$-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

Experience in Adolescents and Adults

[ ]

Postmarketing experience: In extensive worldwide marketing experience with Foradil, serious exacerbations of asthma, including some that were fatal, have been reported. While most of these cases have been in patients with severe or acutely deteriorating asthma (see WARNINGS), a few have occurred in patients with less severe asthma. The contribution of Foradil to these cases could not be determined.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received.

n. Revise the OVERDOSAGE section as follows:

The expected signs and symptoms with overdosage of Foradil are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, ——— Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of Foradil.

Treatment of overdosage consists of discontinuation of Foradil together, with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of Foradil. Cardiac monitoring is recommended in cases of overdosage.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg, ——— the maximum recommended daily inhalation dose in humans on a mg/m^2 basis. The median lethal oral doses in Chinese hamsters, rats, and mice provided even higher multiples of the maximum recommended daily inhalation dose in humans ———

o. Revise the DOSAGE AND ADMINISTRATION section as follows:

[ ]

[ ]

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered.

[redacted]

Additional doses of Foradil should not be used for 12 hours after the administration of this drug. Patients who are receiving Foradil twice daily should not use additional Foradil for prevention of EIB.

[redacted]

p. Incorporate all the relevant information from the PRECAUTIONS-Information for Patients subsection into the Patient's Instructions for Use leaflet.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Pulmonary and Allergy Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

/S/ for

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research