CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-052

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53

for

NDA 22-052

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	TBD
Active Ingredient(s):	Zileuton
Strength(s):	600 mg
Dosage Form:	Controlled-Release Tablet

A. This section should be completed for each individual patent.

1.

U.S. Patent Number: **4,873,529**

Expiration Date: **December 10, 2010**

Type of Patent – Indicate all that apply:

1.	Drug Substance (Active Ingredient)	Yes	X	No	
2.	Drug Product (Composition/Formulation)	Yes		No	X
3.	Method of Use	Yes		No	X

(a) If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: N/A

Name of Patent Owner: Abbott Laboratories

U.S. Agent (if patent owner or applicant does not reside or have a place of business in the U.S.): N/A

2.

U.S. Patent Number: **5,422,123**

Expiration Date: **June 6, 2012**

Type of Patent – Indicate all that apply:

1.	Drug Substance (Active Ingredient)	Yes		No	X
2.	Drug Product (Composition/Formulation)	Yes	X	No	
3.	Method of Use	Yes		No	X

(a) If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: N/A

Name of Patent Owner: Jagotec AG

U.S. Agent (if patent owner or applicant does not reside or have a place of business in the U.S.): N/A

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,422,123 covers the formulation of controlled release tablets. This product is:

___ currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

OR

X the subject of this application for which approval is being sought.

Signed: Roberta Tucker
Date: July 21, 2006
Title: VP Regulatory Affairs
Telephone Number: 781 402 5768

Appears This Way
On Original

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

)A/BLA # : NDA 22-052 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: July 31, 2006 PDUFA Goal Date: May 31, 2007

HFD 570 Trade and generic names/dosage form: Zyflo (zileuton) Controlled Release Tablets

Applicant: Critical Therapeutics, Inc. Therapeutic Class: 3

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- X Yes. Please proceed to the next question.
- ☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: The prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: X Partial Waiver X Deferred ____ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

tudies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see achment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo.__0____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__4___ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr.__4___ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__11__ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- X **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): __06/01/2010__

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

mplete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

CRITICAL Therapeutics

60 Westview Street
Lexington, MA 02421
Phone: (781) 402-5700
Fax: (781) 402-5729

Debarment Certification

This certifies that Critical Therapeutics Inc. has not used in any capacity any person identified by the United States Food and Drug Administration on the recent Debarment List. Subsequent to the conclusion of Study M95-337, Dr. Robert A. Fiddes was placed on the Disqualified/Totally Restricted List For Clinical Investigators on 01 June 1999 and then on the Debarment List on 06 November 2002. Also, Dr. Thomas B. Edwards was placed on the Restricted List for Clinical Investigators on 26 January 1998. The data for Study M95-337 has been examined accordingly, both including and excluding these Investigators.

Further, we certify that Critical Therapeutics Inc. will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

The following is a list of all relevant convictions (for which a person can be debarred) as described in section 306 (a) and (b). The list covers the past five (5) years for persons employed and/or affiliated with Critical Therapeutics Inc (including contractors) and the past thirteen (13) years for persons responsible for the development of data and information to support approval of NDA 22-052 for Zileuton CR.

Person	Date of Conviction	Charge
Robert A. Fiddes	11/06/2002	Conspiring to make false statements to a government agency

Roberta Tucker

Roberta D Tucker, RPh
Vice President
Regulatory Affairs

July 21, 2006

Date

DIVISION DIRECTOR DECISIONAL REVIEW

Date: May 30, 2007

To: NDA 22-052

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy products, CDER, FDA

Product: Zyflo CR (zileuton) extended-release tablets

Applicant: Critical Therapeutics

Administrative and Introduction

Critical Therapeutics submitted a 505(b)(1) new drug application (NDA 22-052) on July 30, 2006, (received on July 31, 2006, CDER stamp date) for use of Zyflo CR (zileuton) extended-release tablets 600 mg for the prophylaxis and chronic treatment of asthma in patients 12 years of age and older at a dose of 1200 mg twice daily. The PDUFA due date for this application is May 31, 2007. Zileuton is a leukotriene synthesis inhibitor. Critical Therapeutics submitted necessary data that support approval of this application. In subsequent sections of this document brief comments are made on findings that have direct bearing on the approvability decision of this application and labeling of this product. For details the reader is referred to Dr. Seymour's summary review, and various primary and secondary discipline reviews.

Regulatory History

The immediate release and extended release formulations of zileuton were originally developed by Abbott Laboratories. The immediate release formulation was approved for marketing in the United States in September 1996 with Abbott Laboratories as the NDA holder (NDA 20-471). Critical Therapeutics acquired ownership of the two products in 2004. The immediate release formulation of zileuton is currently marketed by Critical Therapeutics only in the United States. The extended release formulation is not marketed in any country. When Critical Therapeutics acquired the zileuton products, major development work including pivotal clinical studies with the extended release formulation was already completed by Abbott Laboratories. These clinical studies were conducted in the mid 1990s. The formulation that was originally developed by Abbott Laboratories and used in the pivotal clinical studies was called formulation H. Critical Therapeutics subsequently modified the formulation to formulation E21, which is the to-be-marketed formulation. Critical Therapeutics conducted clinical pharmacology studies with formulation E21 and the immediate release formulation, and attempted to link formulation E21 to formulation H referring to clinical pharmacology studies conducted by Abbott with formulation H and the immediate release formulation. Critical Therapeutics discussed this strategy with the Agency in various interactions including at a pre-NDA meeting on May 2, 2005. The Division found this strategy acceptable.

Chemistry, Manufacturing, and Controls
Zyflo CR is triple layer tablets comprised of an immediate release layer, a middle barrier layer, and an extended release layer. Each tablet contains 600 mg zileuton and various compendial excipients. The immediate release layer disintegrates within minutes and contains mg zileuton, and the extended release layer contains the remaining mg zileuton. The drug substance is manufactured at facilities in and the drug product (tablet cores) are manufactured at and the coated tablets are made at . All DMFs associated with this application are acceptable. All the manufacturing and testing facilities associated with this drug product have acceptable EER status. The CMC review team has found the submitted material adequate to support approval.

There were two major CMC issues identified by the CMC review team early in the review period. First, the dissolution profile of the product that Critical Therapeutics manufactured was different than that originally manufactured by Abbott Laboratories. The difference was determined to be due to different dissolution test methods. Second, there were impurities present in the tablets. Critical Therapeutics tightened the specifications for these impurities to stay within the level qualified by rat toxicology studies.

Nonclinical Pharmacology and Toxicology
Nonclinical pharmacology and toxicology assessment is primarily based on findings for zileuton tablets (NDA 20-471). In various animals the major organs of toxicity were the liver, kidneys, reproductive organs, and hematopoietic system. In 2-year carcinogenicity studies an increase in liver, kidney, and vascular tumors was seen at systemic exposure levels of 5-fold or more than the systemic exposure achieved at the maximum recommended human dose. Although a dose-dependent increase in benign Leydig cell tumor was observed in male rats, Leydig cell tumorigenisis was prevented by replacement therapy with testosterone. The relevancy of this tumor finding to humans is considered limited. Zileuton was negative in a battery of genotoxicity studies. Zileuton had no effects on fertility, but reduced fetal implantation, increased gestation length, prolonged estrous cycle, increased stillbirths, increased skeletal variations, and reduced pup survival and growth, all at exposure levels higher than systemic exposure levels achieved at the maximum recommended human dose. Cleft palates were observed in rabbit fetuses at an oral dose equivalent to the maximum recommended human dose on a mg/m^2 basis.

Clinical Pharmacology
Zileuton is an inhibitor of 5-lipoxygenase and thus inhibits leukotriene LTB4, LTC4, and LTD4 formation. The oral biovailability of zileuton extended-release tablet is significantly increased when taken with food. Therefore, the product is recommended to be taken with food. Zileuton is oxidatively metabolized by CYP1A2, CY2C9, and

CYP3A4, and its elimination is predominantly via metabolism. Dose adjustment in patients with renal impairment or hepatic impairment is not necessary. Zileuton is contraindicated in patients with active liver disease or persistent ALT elevations.

Zileuton has clinically significant drug-drug interactions with theophylline, warfarin, and propanolol, increasing their level when these are taken with zileuton. Dose adjustments of these drugs are necessary when they are co-administered with zileuton. Zileuton may also have interaction with other CYP3A4 inhibitors such as ketoconazole. A thorough QT/QTc study was not conducted with zileuton by Abbott Laboratories or Critical Therapeutics.

A thorough QT/QTc study with zileuton is not necessary because preclinical data is not suggestive of a QT/QTc effect, and there is marketing history of zileuton without any QT prolongation reports.

A major issue with this application is linking of formulation E21 (the to-be-marketed formulation) to formulation H (the original Abbott Laboratories formulation that was used in the pivotal clinical studies). Two studies, study M95-264 (referred subsequently in this document as study 264) and study CTI-03-C05-103 (referred subsequently in this document as study 103) provide such a link, albeit indirectly. Study 264 was conducted by Abbott Laboratories and compared formulation H to immediate release formulation in 23 subjects. Study 103 was conducted by Critical Therapeutics and compared formulation E21 to zileuton immediate release formulation in 24 healthy subjects. The presence of the same zileuton immediate release tablets in both studies gives a common reference to draw some comparative conclusion for the two extended release formulations. Study 264 showed that systemic exposure from formulation H with respect to Cmax, Cmin, and AUC, was approximately 50% compared to immediate release tablets. Study 103 showed that systemic exposure from formulation E21 with respect to Cmax, Cmin, and AUC, were 65%, 105%, and 85%, respectively, compared to immediate release tablets. These two studies suggest that formulation E21 would provide equal or more systemic exposure compared to formulation H, and both would provide lower or similar exposure compared to the immediate release tablets. Therefore, efficacy findings using formulation H can be applied to formulation E21, and safety findings from the zileuton immediate release tablets are relevant to formulation E21.

Clinical and Statistical

General discussion:

The clinical program of zileuton extended-release tablets consisted of two studies, study M95-337A (referred subsequently in this document as study 337), which was a 12 week efficacy and safety study, and study M96-464A (referred subsequently in this document as study 464), which was a 6 month safety study. Clinical studies to support the extended-release tablets were necessary because the systemic exposure from the extended release formulation was less compared to the immediate release formulation. The clinical

program for the extended release formulation was small but reasonable because the immediate release formulation is already approved for the same indication for the same ages. Some characteristics of the pivotal studies are shown in Table 1. The design and conduct of these studies are briefly described, followed by efficacy and safety findings and conclusions.

Table 1. Pivotal clinical studies

ID	Disease	Study type	Study duration	Patient Age, yr	Treatment groups*	n	Study Year#	Countries
337	Asthma	Efficacy and safety	12 week	12 - 81	Z ER 1200 mg BID Z IR 600 mg QID Placebo	199 198 194	1997	USA, 79 sites
464	Asthma	Safety	6 month	12 - 81	Z ER 1200 mg BID Placebo	619 307	1997	USA, 88 sites
* Z ER = zileuton extended release, A IR = zileuton immediate release # Year study ended								

Study 337 was double-blind, placebo-controlled, parallel group in design conducted in patients with asthma 12 to 81 years of age. Patients enrolled in the study were required to have a FEV1 percent predicted 40-75%, FEV1 reversibility of 15%, and taking no asthma medication except a short-acting bronchodilator. The study had a 14-day placebo run-in period followed by a 12-week double-blind treatment period. The primary efficacy variable was FEV1 from spirometry measures, which were done at screening and at treatment days 1, 15, 29, 57, and 85. The primary efficacy endpoint was the mean change in trough FEV1 at 12 weeks for zileuton versus placebo. Secondary efficacy variables included PEFR, rescue short-acting bronchodilator use, asthma symptoms, asthma exacerbations, and asthma QOL questionnaire. Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations.

Study 464 was double-blind, placebo-controlled, parallel group in design conducted in patients with asthma 12 to 81 years of age. Patients enrolled in the study were required to have a FEV1 percent predicted of 40% or more, FEV1 reversibility of 15%, and could be on asthma medications except salmeterol, theophylline, and systemic corticosteroids. Safety was assessed by recording of adverse events, vital signs, clinical laboratory measures, and physical examination.

Efficacy findings and conclusion:

Findings of study 337 along with the known efficacy of immediate release formulation of zileuton support efficacy of zileuton extended-release tablets as a dose of 1200 mg twice daily in patients with asthma 12 years of age and older.

In study 337 zileuton extended-release tablets demonstrated a statistically significant greater improvement compared to placebo in mean change from baseline trough FEV1 at

12 weeks (0.38 L vs 0.27 L, p=0.021). Zileuton extended-release tablets were also superior to placebo at earlier time points for trough FEV1. Rescue short-acting bronchodilator use and PEFR were supportive of efficacy. In this study zileuton immediate release tablets were statistically superior to placebo for the primary endpoints, and the secondary efficacy variables were supportive of efficacy.

Study 464 was also supportive of efficacy. Although study 464 was primarily a safety study, trough FEV1 results showed numerical trends in favor of zileuton compared to placebo.

Safety findings and conclusion:

The safety assessment of zileuton extended-release tablets was based on the two pivotal studies along with findings with zileuton immediate release tablets. In the two controlled studies, there was one death that occurred during the screening period before the patient received zileuton. Serious adverse events and discontinuations due to adverse events were not indicative of any safety signal. The most common adverse events that occurred more in zileuton-treated patients compared to placebo were sinusitis, nausea, and pharyngolaryngeal pain. Because hepatotoxicity is a known adverse reaction with zileuton immediate release tablets, hepatic enzymes were monitored closely in the two studies. Hepatic enzyme elevations were more common in the zileuton treated patients compared to placebo treated patients and the frequency and timing were generally comparable to zileuton immediate release tablets.

The product label for zileuton extended-release tablets will contain hepatic enzyme monitoring frequency that will be identical to the immediate release tablets. Liver injury will be closely monitored in the post-marketing setting by asking the Applicant to expeditiously report spontaneous reports related to liver injury. There is a possibility that market penetration of the extended-release tablets may be higher than the immediate release tablets because of more favorable dosing frequency, which may lead to more adverse event reporting related to hepatotoxicity.

Data Quality, Integrity, and Financial Disclosure

At the pre-NDA stage it was known that one investigator had been debarred and another investigator had been placed on a restricted list, and some clinical sites no longer existed or had no records available for audit because these studies were conducted a long time ago. Because of this knowledge Critical Therapeutics was asked to conduct and submit various sensitivity analyses to assess the effects of these sites on the overall results. Sensitivity analyses conducted by Critical Therapeutics and the Agency did not raise any data integrity concerns. DSI audit of the pivotal clinical sites was not requested. The Division initially requested DSI audit for the site that conducted clinical pharmacology study. The site was located in [redacted]. The Division later determined that inspection of that site was not critical because of the findings of the clinical studies that form the primary basis of approval of this application.

There were no ethical issues. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements.

Pediatric Considerations
Critical Therapeutics requested a deferral of studies for children 4 to 11 years of age and a waiver for children below 4 years of age. This request is reasonable and will be granted. For an oral asthma controller medication, such as montelukast, the Division has asked for studies in children down to 6 months of age. However, zileuton is eliminated via glucuronidation in the liver and it is known that glucuronide formation reaches adult values between the third and fourth year of life. Therefore, the metabolism of zileuton in children less than 4 years of age may be unpredictable, which may increase the possibility of hepatotoxicity. Zileuton is known to be associated with hepatotoxicity and there are alternative products available for asthma controller therapy in children below 4 years of age, such as inhaled corticosteroids, and oral montelukast.

Labeling
Critical Therapeutics submitted a label in the Physician's Labeling Rule format that generally contains information consistent with the zileuton immediate release tablets and other products of this class. The label was reviewed by various disciplines of this Division, and on consult by OSE and DDMAC. Various changes to different sections of the label are recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and Critical Therapeutics have agreed to the final version of the label.

Product Name
Critical Therapeutics originally intended to the use the trade name [redacted] for this product, but during the review period changed the proposed trade name to Zyflo XR. The root name, Zyflo, was found to acceptable by OSE and DMETS, but the XR extension was not found to be acceptable. The extension XR has traditionally been used for products dosed once daily, and there was potential confusion with Zyvox, which is another product (an antibiotic) that also comes in 600 mg strength. Critical Therapeutics subsequently changed the trade name to Zyflo CR, which was determined to be acceptable by DMETS. The Division noted that although the modifier was changed to CR, the dosage form should remain extended-release as controlled release is not an acceptable dosage form. Therefore, the product name will be Zyflo CR (zileuton) extended-release tablets.

Action
Critical Therapeutics has submitted adequate data to support approval of zileuton extended-release tablets for the prophylaxis and chronic treatment of asthma in patients 12 years of age and older. The action on this application will be Approval.

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

/s/

Badrul Chowdhury
5/30/2007 04:18:33 PM
MEDICAL OFFICER

NDA 22-052: ZYFLO CR™ (zileuton) controlled-release tablets
Formerly ZYFLO XR™ (zileuton extended-release tablets)

May 29, 2007

Badrul A. Chowdhury, M.D., Ph.D., Director
Division of Pulmonary and Allergy Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

RE: Response to May 25, 07 labeling comments
Response to May 25, 07 DMETS comments

Reference is made to the Division's labeling comments received on Friday, May 25, 2007, and to the Division of Medication Errors and Technical Services (DMETS) comments conveyed by Anthony Zeccola on May 25, 2007. Attached please find our responses to both sets of comments along with revised prescribing information for your consideration.

Labeling Comments

General comments:

1. **Adjust the formatting of the Highlights and Contents sections to fit on a single page. The Highlights should be limited to half a page in length.**

We have revised the labeling as requested.

2. **Insert a solid line between the Table of Contents (TOC) and the FPI similar to the line between the Highlights and the TOC.**

We have revised the labeling as requested.

3. **The date of initial U.S. Approval was changed to 1996 because the date should be the first time the molecular entity was approved.**

Acknowledged.

4. **The warning regarding not using ZYFLO XR to treat an acute asthma attack was moved to the Indications and Usage Section as this is a limitation in the use of Zyflo XR.**

Acknowledged.

5. **Regarding Figure 1 in Section 14 (Clinical Studies), it appears that the figure represents a LOCF analysis of the data. Clarify if this is the case and if so, why are the number of subjects at Week 2 different from the rest of the timepoints.**

Yes, Figure 1 presently in the attached proposed PI represents an LOCF analysis of the data. Missing values were imputed by carrying forward the last observation from a double-blind treatment visit. Baseline observations were not carried forward to impute missing treatment visit data. The number of patients at Week 2 was different from the rest of the timepoints because for 3 patients in the ZYFLO CR group and 1 patient in the Placebo group, the Week 2 FEV_1 data were missing but the Week 4 FEV_1 data were available in the database. The missing Week 2 FEV_1 data were not imputed using the LOCF methodology because there were no on-treatment measurements that could be carried forward for this purpose.

6. **If figure 1 is an LOCF analysis of the data, submit a figure displaying the results with the observed data for us to determine which figure is most appropriate for the product label. The figure should have the same format except change the x axis to represent weeks, not days. If you are unable to provide the figure with the observed data, we may request that figure 1 be removed from the label.**

Below are two additional versions of Figure 1. Both display results with the as-observed data with the x-axis in weeks.

Figure 1 A depicts the as-observed data (without LOCF); Figure 1 B contains the as-observed data and has, in addition, the Endpoint (i.e., the last observation carried forward). Figure 1 B is very similar to the approach taken in the Advair® PI. We have put the asterisk for statistical significance below the Endpoint because that was the primary efficacy variable in the 12-week clinical trial in patients with asthma.

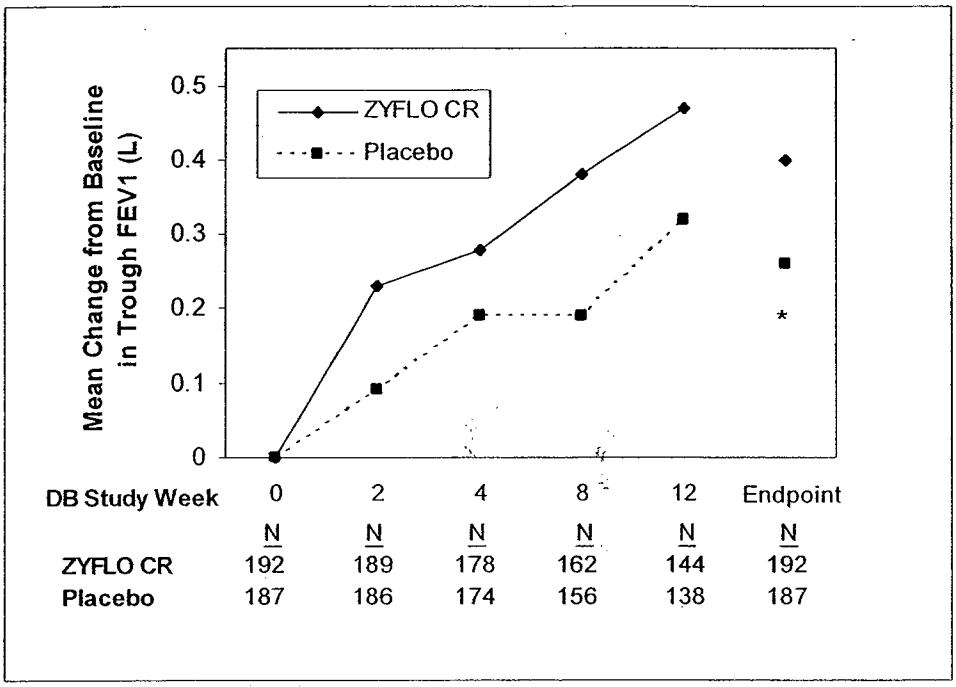
We request that the Division decides which figure is most appropriate for the ZYFLO CR. We commit to inserting the figure the Division deems most appropriate.

FIGURE 1 A

RESULTS OF ANALYSIS OF CHANGES FROM BASELINE IN FEV1 TO THE PRE-DOSING VALUE BY DOUBLE-BLIND STUDY WEEK (FULL ANALYSIS SET WITHOUT LAST OBSERVATION CARRIED FORWARD METHODOLOGY)

Figure 1 B

RESULTS OF ANALYSIS OF CHANGES FROM BASELINE IN FEV1 TO THE PRE-DOSING VALUE BY DOUBLE-BLIND STUDY WEEK (FULL ANALYSIS SET WITHOUT LAST OBSERVATION CARRIED FORWARD METHODOLOGY) PLUS RESULTS FROM THE ENDPOINT ANALYSIS (FULL ANALYSIS SET WITH LAST OBSERVATION CARRIED FORWARD METHODOLOGY)



DB Study Week	0	2	4	8	12	Endpoint
	N	N	N	N	N	N
ZYFLO CR	192	189	178	162	144	192
Placebo	187	186	174	156	138	187

*p ≤0.050

Comments specifically pertaining to the Patient Package Insert:

7. **Unless Zyflo XR is dispensed in unit-of-use packaging with the PPI enclosed, it is unlikely the patients will ever receive the PPI. Explain the plan for ensuring that patients receive the PPI.**

ZYFLO CR will be supplied to pharmacies as a 120-count trade bottle. This presentation will have a copy of the full prescribing information for ZYFLO CR affixed to the top of the bottle. The full prescribing information contains a copy of the patient prescribing information. The 120-count trade bottle was chosen because it represents a full 30-day supply of the medication, which is how we expect the vast majority of prescriptions to be written and filled.

In addition to the attachment of the prescribing information to the top of all bottles, each pharmacy is required to provide patient information with all prescriptions, both new and refills. Every pharmacy licensed by the Board of Pharmacy and having a NABP (National Association of Boards of Pharmacy) number must be in compliance. The patient information provided is found in computer databases that

supply important information about the product. CRTX will work directly with these database vendors as the information for ZYFLO CR is being added, to ensure that the complete patient prescribing information is what is used in the databases and thus provided to patients when filling their prescription.

8. **We have deleted the section "[redacted]' This section is used to convey to patients important safety information from a bolded or boxed warning; this does not apply to the Zyflo XR label. The proposed information from this section has been moved to the section "How should I take Zyflo XR?"**

Acknowledged.

9. **Provide instruction on how patients should handle a missed dose. Also include this information in the Dosage and Administration Section of the package insert.**

We have added the following statement to the PPI section of the package insert: "If you miss a dose, just take your next scheduled dose when it is due. Do not double the dose." Similar instructions have been added to Section 2, Dosage and Administration, and Section 17.1, Information for Patients.

10. **We have modified the Patient Package Insert to address the most serious side effects first.**

Acknowledged.

11. **Include website and phone information for patients.**

Website and phone information have been added for the patients.

In addition, per the DMETS comments discussed below, we have changed ZYFLO XR to ZYFLO CR throughout the labeling.

Other changes to the insert include:

- Addition of phonetic spelling of ZYFLO to Section 17.2
- Instructions on handling a missed dose have been added to Section 17.1 in addition to the two sections requested by FDA, i.e., Section 17.2 and Section 2
- Under Section 12.3 Pharmacokinetics, for consistency, we have changed the confidence internals for Cmax [redacted] to decimals to match how the confidence intervals for the AUCs (decimals) are presented.

- Under Section 6.1 Short-Term Studies Experience Table 1, we have updated the column headers to further clarify the information presented in the table (i.e., replacing the "% Incidence" with "n (%)". This update is based on the format used in the Advair® label.

We have also made minor editorial changes to ensure consistent spacing, punctuation, etc. All changes are shown in tracked-changes mode.

DMETS Comments

1. While the XR modifier is unacceptable, other modifiers might be acceptable. The Applicant agreed to suggest another modifier and submit it for Agency review.

We propose the name ZYFLO CR™ (zileuton) controlled-release tablets. All labeling (including the package insert) will be revised to reflect this naming convention pending FDA approval.

2. Because the immediate release product's tablets contain the same dosage strength, the Applicant agreed to include a statement indicating the dosing schedule on the principal display panel (located at the bottom of the principal display panel).

We commit to revise the labels as follows:

2 Tablets BID

will be printed and located near the bottom of the principal display panel.

3. The Applicant agreed to an educational campaign as a means of highlighting the differences between the two products.

Our marketing campaign for ZYFLO CR will include an educational campaign for both health care providers and patients highlighting the differences between the two products.

4. Once the Applicant submits a proposed alternative modifier, the Agency will review their proposal and provide appropriate comments.

We have proposed CR (controlled-release) as the modifier. Specifically, the name we are proposing is:

ZYFLO CR™
(zileuton) controlled-release tablets

5. Additional DMETS comments regarding the carton and container label were conveyed as follows:

A. General Comments

(i) Relocate the net quantity so that it is not presented in close proximity to the product strength. Postmarketing evidence demonstrates that confusion between the net quantity and product strength may occur if they are presented in close proximity to one another.

We commit to revising the labels as requested.

(ii) Revise the presentation of the proprietary name so that the entire name is presented in the same font color. As currently presented, the root name (Zyflo) is presented with more prominence than the modifier (XR), which may lead to the modifier being missed.

We propose the following:

ZYFLO CR™
(zileuton) controlled-release tablets

(iii) Revise the "[redacted]" statement to read "Usual Dosage: See package insert."

We commit to revising the labels as requested.

B. Container Label (Sample, 20 tablets)

(i) See General Comments

We acknowledge your comments and commit to revising the Sample Container label accordingly.

(ii) Relocate the "Sample: Not For Resale" statement to the principal display panel.

We commit to revising the labels as requested.

C. Container Label (Trade, 120 Tablets)

(i) See General Comments

We acknowledge your comments and commit to revising the Sample Container label accordingly.

(ii) Per 21 CFR 201.10(g)(2), increase the prominence of the established name so that it is at least ½ the size of the proprietary name.

We commit to increasing the prominence of the established name so that it is at least ½ the size of the proprietary name.

35 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Products
HFD-570

Through: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Acting Team Leader
Division of Medication Errors and Technical Support, HFD-420

Date: May 29, 2007

OSE Review # 2007-1213, Zyflo CR (Zileuton Extended-release Tablets)
600 mg
NDA# 22-052

This memorandum was written in response to a request from the Division of Pulmonary and Allergy Products (HFD-570), to review the proprietary name Zyflo CR. The sponsor initially submitted the name Zyflo XR. However DMETS objected to the use of the proposed name Zyflo XR due to the potential for look-alike/sound-alike confusion with Zyvox in addition to the fact that the modifier 'XR' is generally used to communicate once-daily dosing, not twice-daily dosing as is the case with Zyflo XR.

Limited data was available to complete a comprehensive analysis of the proprietary name, Zyflo CR because of the PDUFA date of May 31, 2007. Thus, due to the high priority nature of this review, the routine analysis was not performed. The DMETS' safety evaluator was only able to conduct a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Zyflo CR to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The proposed name was not discussed during an Expert Panel Discussion, and Prescription Studies were not conducted regarding Zyflo CR. Additionally, the Division of Drug Marketing, Advertising, and Communication (DDMAC) was not consulted from a promotional perspective with regard to the name Zyflo CR. However, DMETS will conduct an examination of the "CR": modifier, assess the potential for product line confusion and assess whether the addition of the modifier will increase thee potential for Zyflo Cr to look or sound similar to currently marketed products.

A. Examination of the "CR" modifier

To evaluate the potential of medication error with the proposed name of Zyflo CR, DMETS reviewed aspects that commonly lead to error when product extensions are introduced in the marketplace that include: what will happen if the modifier CR is omitted, what does the addition of the modifier do to the visual presentation or phonetic pronunciation of the name, can the modifier be misinterpreted, is the modifier meaningful, and what is the potential for confusion with the currently marketed Zyflo product line, and the

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[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

potential for proprietary name confusion with drug products currently marketed.

1. In analysis of the potential for the "CR" modifier to resemble any numbers, dosing instructions, or medical abbreviation, DMETS does not believe "CR" could be confused as a letter, number (i.e. 600 mg), or misinterpreted as dosing instructions. DMETS notes that the abbreviation does not appear on the dangerous abbreviations list. The modifier "XR" is identified by standard references[4] as calculation rate, calculus removed, calorie restricted, cardiac rehabilitation, cardiac resuscitation, cardiac rhythm, cardio respiratory, cardiorrhexis, caries resistant, cartilage residue, case report, cathode ray, cellular receptor, centric relation, chemoradiation, chest and right arm, chest roentgenogram, chief resident, chloride, choice reaction, chromium, chronic rejection, clinical record, clinical remission, clinical research, closed reduction, clot retraction, cob orectal, coefficient of fat retention, colon resection, colonization resistance, colony reared, colorectal, community relations, complement receptor, complement regulatory, complete recanalization, complete remission, complete response, computed radiography, computed radiology, conditioned reflex, conditioned response, congenital rubella, congo red, contact record, control room, controlled respiration, controlled-release, conversion rate, cooling rate, cortico resistant, cranial, creatinine, cremasterreflex, cresyl red, critical ration, crown rump, calcification rate, and chromium. However, these interpretations should not result in confusion. Despite the potential for the "CR" modifier to look or be defined as above, DMETS does not believe this would prohibit the use of this modifier.

3. When evaluating the appropriateness of the modifier and the intended meaning, we discovered there are currently thirteen drug products containing the modifier "CR". Of these thirteen, the following eight products and their approval dates are listed in the Orange Book: Paxil CR (1999), Coreg CR (2006), Ambien CR (2005), Dynacirc CR(1994), Afeditab CR, Sinemet CR (1991), Norpace CR (1982), and Eskalith CR (no longer marketed, 1982). Additionally, five proposed drug products were identified that include Luvox CR***, Dilaudid CR***, Topiramate CR***, Vicodin CR*** and Requip CR***.

   Nine of the thirteen "CR" products have once daily dosing (Paxil CR, Coreg CR, Ambien CR, Dynacirc CR, Afeditab CR, Luvox CR***, Dilaudid CR***, Topiramate CR***, and Requip CR***), while the remaining four products (Sinemet CR, Eskalith CR, Norpace CR, and Vicodin CR***) are dosed twice daily. Thus, there are both once daily and twice daily dosing frequencies associated with the "CR" modifier.

   One can conclude that for recent approvals "CR" infers daily dosing, but overall the modifier relates to both daily and twice daily dosing. Thus, there is no specific dosing interval or interpretation associated with the "CR" modifier. Since Zyflo CR will be dosed two times a day the CR modifier may be the preferred choice for the proposed product, as it is not directly associated with a dosing frequency or dosing regimen.

   In addition, to avoid ambiguity over the dosing regimen, it is imperative that the "Twice Daily Dosing" statement be prominently presented on all Zyflo CR labels and labeling, and as well as any related marketing material, in order to prevent confusion. Because the modifier CR can have several meanings, this may be the best method to assure practitioners research the correct dosing regimen and avoid assumptions of frequency leading to medication error. DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation.

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[4] http://www.pharma-lexicon.com/, 02May2007.

*** Proprietary and confidential information that should not be released to the public.

B. Potential for Product Line Confusion

Post-marketing experience has shown that the introduction of product line extensions result in medication errors especially when there is any overlap in product characteristics and a knowledge deficit with respect to the introduction of the new extended-release formulation. Errors introduced by product line extensions are known to occur at all points in the medication use process. With respect to Zyflo CR, DMETS is concerned with the potential omission of the 'CR' modifier, overlapping strengths, and shelf/computer selection errors between Zyflo & Zyflo CR.

1. Omission of the "CR" modifier

Post-marketing experience has shown that the introduction of product line extensions result in medication errors when the modifier is omitted[5]. In this case, if the CR modifier is omitted it is almost certain that Zyflo will be dispensed because of the overlapping product characteristics. Zyflo CR and Zyflo overlap in established name (zileuton), indication of use (asthma), route of administration (oral), and dosage form (tablet). Additionally, both products are supplied as 600 mg tablets with a total daily dose 2400 mg.

By choosing to develop an extended-release formulation of zileuton tablets that overlaps with the strength of the currently marketed immediate-release formulation (600 mg), the Sponsor has eliminated a potentially valuable error-reduction strategy that has been employed in other product line extensions. DMETS suggests an alternative approach such as the strategy used for the Paxil CR line with strengths of 12.5 mg, 25 mg, 37.5 mg compared to the existing Paxil strengths of 10 mg, 20 mg, 30 mg, and 40 mg. Thus, if the modifier were omitted or overlooked, the difference introduced by the strength offers an opportunity for an error to be caught before it reaches the patient. In the case of Zyflo, there will be nothing to distinguish these products. Thus the sponsor could and should have chosen a small deviation in strength similar to Paxil CR to lessen confusion.

If Zyflo and Zyflo CR confusion were to occur, the outcome must be considered. The likely cause of this confusion would be due to the omission of the modifier or knowledge deficit that the new formulation exists, which would result in the patient receiving an immediate-release tablet twice daily rather than four times daily. Thus, the patient would not receive the expected total day zileuton coverage with potential fluctuations in blood levels resulting in adverse events.

Thus, we believe this confusion will occur based on the possibility of omission of the suffix, product characteristic overlap, and a knowledge deficit of the new product. Education alone will not fully address this confusion and we strongly recommend the sponsor revise the product strengths so that they do not overlap. However, since this does not appear to be a viable option due to the pending approval, DMETS recommends a low leverage approach to minimizing this confusion. It is imperative that the "Twice Daily Dosing" statement be prominently presented on all Zyflo CR labels and labeling, and as well as any related marketing material, in order to prevent confusion.

2. Shelf and Computer Selection Errors

Typically, pharmaceutical products are organized alphabetically by proprietary name, established name, or sorted by manufacturer. Since these attributes are identical with the currently marketed Zyflo product line and the proposed Zyflo CR, it is likely that the products will be stored near one another in virtually any organization carrying both product lines. Thus, this proximity could lead to selection errors, especially if the container labels look the same. Additionally, due to the shared root name of "Zyflo",

[5] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

there is a possibility for computer selection errors. In order to minimize this potential source of confusion, differentiation in the packaging and labeling of Zyflo and Zyflo CR is essential.

Overall, DMETS believes that labeling and packaging differentiation will help to minimize the potential for product selection errors, but will not be able to fully avoid confusion between Zyflo and Zyflo CR. Thus, DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation to avoid overdosing (and subsequent adverse events). In addition, to avoid ambiguity over the dosing regimen, it is imperative that the "Twice Daily Dosing" statement be prominently presented on all Zyflo CR labels and labeling, and as well as any related marketing material, in order to prevent confusion.

C. Look-Alike and Sound-Alike Concerns

In reviewing the proprietary name Zyflo XR, the names identified to have visual and phonetic similarity to Zyflo CR are Zyvox, Effexor, Zyflux, and Zocor, and the medical term heplock. However, since a comprehensive name review could not be conducted due to time constraints, this list may not be inclusive of all names with look-alike and/or sound-alike potential.

In the initial analysis of the five names it was determined that four names, Effexor, [redacted], and Zocor, and the medical term heplock would not be considered further for the following reasons.

- Lack of significant orthographic and or phonetic similarities
- Effexor and Zocor do not share product commonalities with Zyflo CR such as dosage form, route of administration, product strength, usual dose, and/or indication of use.
- The name [redacted]* was a proposed name for a product that was the subject new drug application, however, the name was not used.
- Heplock is a medical term which is unlikely to be confused with the proposed name when Zyflo CR is used in conjunction with the product strength and/or desired dose.

As stated in OSE Consult 2007-545, dated May 24, 2007, there has been postmarketing confusion between Zyflo and Zyvox. Given this existing confusion and overlapping product characteristics, DMETS believes that it is possible that confusion may occur between Zyvox and Zyflo CR, despite the addition of the modifier. Thus DMETS recommends continued monitoring for postmarketing medication errors due to name confusion between Zyflo CR and Zyvox.

In summary, DMETS does not object to the use of the proprietary name, Zyflo CR. Additionally, DMETS recommends the label and labeling revisions communicated in OSE Consult 2007-545, dated May 24, 2007. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Nancy Clark at 301-796-1187.

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/s/

Kristina Arnwine
5/30/2007 04:03:56 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/30/2007 04:12:02 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: May 25, 2007

TIME: 12:00 Noon

APPLICATION: NDA 21-052 Zyflo XR

FDA Representative:

Anthony M. Zeccola, M.A., Senior Regulatory Management Officer

Critical Therapeutic Representative:

Roberta Tucker, R.Ph, Vice President, Regulatory Affairs

Background

This teleconference took place as a result of regulatory recommendations made by the Division of Medication Errors and Technical Services (DMETS) in their tradename review of "Zyflo XR" (zileuton extended release tablets), dated May 23, 2007. In their review DMETS noted that the XR modifier to the Zyflo tradename is not acceptable. This finding is based on the fact that with the exception of a few monograph products, XR is generally accepted as meaning a once a day dosing schedule, this product is intended for twice a day dosing.

Discussion

1. While the XR modifier is unacceptable, other modifiers might be acceptable. The Applicant agreed to suggest another modifier and submit it for Agency review.

2. Because the immediate release product's tablets contain the same dosage strength, the Applicant agreed to include a statement indicating the dosing schedule on the principle display panel (located at the bottom of the principle display panel).

3. The Applicant agreed to an educational campaign as a means of highlighting the differences between the two products.

4. Once the Applicant submits a proposed alternative modifier, the Agency will review their proposal and provide appropriate comments.

5. Additional DMETS comments regarding the carton and container label were conveyed as follows:

   A. General Comments

i. Relocate the net quantity so that it is not presented in close proximity to the product strength Postmarketing evidence demonstrates that confusion between net quantity and product strength may occur if they are presented in close proximity to one another.

ii. Revise the presentation of the proprietary name so that the entire name is presented in the same font color. As currently presented, the root name (Zyflo) is presented with more prominence than the modifier (XR), which may lead to the modifier being missed.

iii. Revise the "[redacted] statement to read "Usual Dosage: See package insert".

B. Container Label (Sample, 20 tablets)

i. See General Comments.

ii. Relocate the "Sample. Not for Resale" statement to the principal display panel).

C. Container Label (Trade, 120 Tablets)

i. See General Comments.

ii. Per CFR 21 201.10(g)(2), increase the prominence of the established name so that it is at least ½the size of the proprietary name.

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/s/

Anthony Zeccola
5/25/2007 12:30:15 PM
CSO

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Memorandum of Telephone Facsimile Correspondence

Date: May 25, 2007

To: Roberta Tucker

Fax No.: 781-402-5728

From: Anthony M. Zeccola

Subject: FDA Label Comments
NDA 22-052 Zyflo (zileuton controlled-release) Tablets

Number of Pages: 17 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

See appended electronic signature page

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

These are recommendations regarding the Zyflo controlled-release product label, additional recommendations may follow.

We have provided a copy of the labeling with revisions in redline/strikeout. The following comments describe the major revisions and the reasons for the changes.

General comments:

1) Adjust the formatting of the Highlights and Contents sections to fit on a single page. The Highlights should be limited to half a page in length.
2) Insert a solid line between the Table of Contents (TOC) and the FPI similar to the line between the Highlights and TOC.
3) The date of initial US Approval was changed to 1996 because the date should be the first time the molecular entity was approved.
4) The warning regarding not using Zyflo XR to treat an acute asthma attack was moved to the Indications and Usage Section as this is a limitation in the use of Zyflo XR.
5) Regarding Figure 1 in Section 14 (Clinical Studies), it appears that the figure represents a LOCF analysis of the data. Clarify if this is the case and if so, why are the number of subjects at Week 2 different from the rest of the timepoints.
6) If figure 1 is an LOCF analysis of the data, submit a figure displaying the results with the observed data for us to determine which figure is most appropriate for the product label. The figure should have the same format except change the X axis to represent weeks, not days. If you are unable to provide the figure with the observed data, we may request that figure 1 be removed from the label.

Comments specifically pertaining to the Patient Package Insert:

7) Unless Zyflo XR is dispensed in unit-of-use packaging with the PPI enclosed, it is unlikely that patients will ever receive the PPI. Explain the plan for ensuring that patients receive the PPI.
8) We have deleted the section "[redacted]". This section is used to convey to patients important safety information from a bolded or boxed warning; this does not apply to the Zyflo XR label. The proposed information from this section has been moved to the section, "How should I take Zyflo XR?"
9) Provide instruction on how patients should handle a missed dose. Also include this information in the Dosage and Administration Section of the package insert.
10) We have modified The Patient Package Insert to address the most serious side effects first.
11) Include website and phone information for patients.

14 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Anthony Zeccola
5/25/2007 04:17:49 PM
CSO

MEMORANDUM

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

DATE: May 21, 2007

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products

VIA: Anthony Zeccola, Regulatory Management Officer
Division of Pulmonary and Allergy Products

FROM: Sharon R. Mills, B.S.N., R.N., C.C.R.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for NDA# 22-052 Zyflo XR (zileuton extended-release tablets), RCM #2007-1005.

Background and Summary

Critical Therapeutics, Inc. submitted a new NDA on July 31, 2006 for Zyflo XR (zileuton extended-release tablets). Zyflo XR (zileuton extended-release tablets) is a leukotriene synthesis inhibitor with the proposed indication for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older. Included in the proposed labeling is patient labeling in the form of a Patient Package Insert (PPI).

See the attached PPI for our recommended revisions to the sponsor's proposed PPI. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. We have put this PPI in the patient-friendly format (specified in 21CFR 208.20) that we are recommending for all FDA approved patient labeling, although this format is not required for drug products with voluntary PPIs like Zyflo XR. These recommended changes are consistent with current research to improve risk communication to a broad range of audiences including those with lower levels of literacy.

These revisions are based on the proposed Professional Information (PI) submitted on July 31, 2006 and revised by the Review Division on May 3, 2007. Patient labeling should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations

1. A PPI for Zyflo XR is voluntary. Unless Zyflo XR is dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will ever receive the PPI. The sponsor states in the PI that the product is available in bottles of 120 tablets. The sponsor should explain their plan for ensuring that patients receive the PPI.

2. The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 7.9, and a Flesch Reading Ease Score of 60.7. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level.) The reading scores as submitted by the sponsor are acceptable. However, we have simplified the wording where possible, made it consistent with the Professional Information (PI) and removed unnecessary information.

3. The section ' [redacted] ' has been deleted. This section is used to convey to patients important safety information from a bolded or boxed warning; this does not apply to the Zyflo XR label. The proposed information from this section has been moved to the section, "How should I take Zyflo XR?"

4. We concur with the comments from DDMAC dated March 22, 2007 regarding language in Sections 17.1 of the PI, *Information for Patients*, and 17.2, *FDA-Approved Patient Labeling*. The PPI has been modified accordingly.

5. Since allergic reactions are possible with this product and not hypothetical, the sponsor should list the possible symptoms of allergic reactions that have been seen with ZYFLO XR. The Contraindications section of the PI, lists "(e.g., rash, eosinophilia, etc.)". The list should be made more complete and there should be equivalent language in the PI and PPI. The PPI language should be patient-friendly and should not include abbreviations such as "e.g.". The PPI sections that should be addressed are "Who should not take Zyflo XR?" and "What are the possible side effects of Zyflo XR?"

6. There is an approved PPI for Zyflo NDA# 20-471 which is appended to the currently approved label, dated September 28, 2005. There are a number of differences between this approved PPI and the proposed PPI for Zyflo XR, and we recommend to the extent possible, that the Zyflo PPI be revised to be consistent with the final Zyflo XR PPI.

Comments to the review division are ***bolded, underlined and italicized*** in the attached document. We are providing to the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

Please let us know if you have any questions.

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✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Sharon Mills
5/21/2007 03:57:23 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
5/21/2007 05:33:14 PM
DRUG SAFETY OFFICE REVIEWER

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-052 Supplement # Efficacy Supplement Type SE-

Proprietary Name: [redacted]CR
Established Name: **zileuton**
Strengths: **Controlled-Release Tablets 600mg**

Applicant: **Critical Therapeutics, Inc.**
Agent for Applicant (if applicable):

Date of Application: **7/30/06**
Date of Receipt: **7/31/06**
Date clock started after UN:
Date of Filing Meeting: **9/21/06**
Filing Date: **9/29/06**
Action Goal Date (optional): User Fee Goal Date: **5/31/07**

Indication(s) requested: Prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

Type of Original NDA:	(b)(1) **X**	(b)(2) ☐
AND (if applicable)		
Type of Supplement:	(b)(1) ☐	(b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S **X** P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES **X** NO ☐
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO **X**

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO **X**
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☐ NO **X**
  If no, explain:

- Was form 356h included with an authorized signature? YES ☐ NO **X**
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☐ NO **X**
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES **X**

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☐ NO ☐
- Exclusivity requested? YES, X Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES **X** NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO **X**
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES **X** NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO **X**

  If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES **X** NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES **X** NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES **X** NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND 47, 561, IND 30, 661
- Are the trade, established/proper, and applicant names correct in COMIS? YES **X** NO ☐
  If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) May 2, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES X NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES X NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES X NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES **X** NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9/21/06

NDA #: 22-052

DRUG NAMES: ~~—~~ CR

APPLICANT: Critical Therapeutics

BACKGROUND: This is a controlled-release version of zileuton tablets, approved under NDA 20-471.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Badrul Chowdhury, Sakky Seymour, Susan Limb, Jean Wu, Joe Sun, Martin Haber, Prasad Peri, Stephen Moore, Shinja Kim, Tay Fadiran, Jim Gebert, Ruthie Davi

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Limb
Secondary Medical:	Seymour
Statistical:	Gebert
Pharmacology:	Wu
Chemistry:	Shaw
Biopharmaceutical:	Kim
Microbiology, sterility:	
DSI:	
OPS:	
Regulatory Project Management:	Zeccola
Other Consults:	

Per reviewers, are all parts in English or English translation? YES **X** NO ☐
If no, explain:

CLINICAL FILE **X** REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO **X**

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A **X** YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☐	FILE	**X**	REFUSE TO FILE	☐	
STATISTICS	N/A ☐	FILE	**X**	REFUSE TO FILE	☐	
BIOPHARMACEUTICS		FILE	**X**	REFUSE TO FILE	☐	

- Biopharm. study site audits(s) needed? YES ☐ NO ☐

PHARMACOLOGY/TOX	N/A ☐	FILE	**X**	REFUSE TO FILE	☐	

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY		FILE	**X**	REFUSE TO FILE	☐	

- Establishment(s) ready for inspection? YES **X** NO ☐
- Sterile product? YES ☐ NO **X**
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- **X** Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☐ Convey document filing issues/no filing issues to applicant by Day 74.

Anthony M. Zeccola
Regulatory Project Manager

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/s/

Anthony Zeccola
5/17/2007 11:09:08 AM
CSO

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Memorandum of Telephone Facsimile Correspondence

Date: May 10, 2007

To: Roberta Tucker

Fax No.: 781-402-5728

From: Anthony M. Zeccola

Subject: FDA Label Comments
NDA 22-052 [redacted](zileuton) Controlled-Release Tablets

Number of Pages: 14 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

See appended electronic signature page.

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

These recommendations regarding the Zyflo XR product label are based on our teleconference that took place on May 3, 2007. Due to the new labeling format and outstanding labeling consults, additional recommendations will follow.

We have provided a copy of the labeling with revisions in redline/strikeout. The following comments describe the major revisions and the reasons for the changes.

1) After further discussion, we consider "hepatotoxicity" to be the most appropriate term to describe the hepatic events observed in the clinical trials for Zyflo XR and Zyflo and in post-marketing reports. Transaminitis and hyperbilirubinemia are laboratory abnormalities that are markers of hepatotoxicity. Other terms, such as "liver dysfunction," imply abnormalities of hepatic synthesis or metabolism, such as coagulopathy or impaired ammonia clearance.
2) [redacted] are discussed in Section 6.2, Long-term Clinical Studies Experience and have been removed from Section 6.1, since the white count abnormalities were observed primarily in Study M96-464.
3) In Section 11, the terms "[redacted] and "[redacted]" are promotional in tone and have been replaced by "immediate-release" and "extended-release."
4) Re-format Figure 1 to clarify the number of patients assessed at each time point. Refer to the Advair® label for an example of preferred formatting.
5) Provide the percentage of males in Study M95-337 in Sections 6.1 and 14.
6) Include a statement in the Full Prescribing Information about the proper administration of the zileuton ER tablet (no cutting, chewing, or crushing of tablet).
7) Adjust the formatting of the Highlights and Contents sections to fit on a single page.
8) Provide a table of all adverse events ranked by incidence using MedDRA preferred terms for Study M95-337 and a separate table for M96-464. The current NDA has a table for the studies combined. The individual study reports contain adverse event data using MedDRA terms for those events occurring ≥3%; the tables containing all adverse events in the individual study reports use COSTART terms.

11 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Anthony Zeccola
5/10/2007 11:55:36 AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Nancy Clark **Division of Drug Surveillance, Research, and Communication Support (DSRCS)**	**Anthony Zeccola** **Regulatory Management Officer** **DPAP, HFD-570**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/3/07		**22-052**	N	7/31/07

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zyflo (zileuton) Extended Release	S	3	**ASAP**

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*: **PPI Review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: PPI Review – See attachment for latest version of the label (Word version will be sent via e-mail)

PDUFA DUE DATE: May 31, 2007

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Anthony M. Zeccola 301-796-1318	**DFS Only**
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Anthony Zeccola
5/3/2007 06:00:18 PM

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Memorandum of Telephone Facsimile Correspondence

Date: May 1, 2007

To: Roberta Tucker

Fax No.: 781-402-5728

From: Anthony M. Zeccola

Subject: FDA Label Comments
NDA 22-052 [redacted] (zileuton) Controlled-Release Tablets

Number of Pages: 19 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

See appended electronic signature page

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

These are preliminary recommendations regarding the Zyflo XR product label. Due to the new labeling format and outstanding labeling consults, additional recommendations will follow.

We have provided a copy of the labeling with revisions in redline/strikeout. The following comments describe the major revisions and the reasons for the changes.

Highlights
Changes made to Highlights include the addition of instructions for the health care provider for the Warnings and Precautions and for the Drug Interactions.

Contraindications (4)
"[redacted]" was deleted because patients with elevated hepatic function enzymes should not use Zyflo XR, regardless if there is an explanation for the elevation.

Warnings and Precautions (5)
Information regarding the clinical data from the Zyflo program was moved from the Adverse Reactions section (6) to this section. However, before including in the label, clarify how the 3.2% was determined so we can more accurately describe the findings in the label.

Adverse Reactions (6)

- Introduction added regarding Hepatotoxicity and common adverse reactions to be consistent with the new PLR format.
- Results of the 12 week study and the 6 month study are described separately in this section. Insert values for the Xs in this section.
- Delete the [redacted] from the table and construct a new table with the adverse reactions with >5% incidence and > placebo in the 12 week study.
- A post-marketing experience section (6.3) was added to include the cases of severe hepatic injury reported.

Special Populations (8)

- Information was deleted from the [redacted] because the proposed indication is for adults and adolescents > 12 years old; therefore, we do not want information regarding children < 12 years of age in the label.
- Details regarding renal and hepatic impairment PK were moved to the PK section (12.3). Sections 8.6 and 8.7 should contain the broad clinical recommendations.

Clinical Pharmacology (12)
Add the age range and mean age to the description of the population in the two clinical pharmacology studies described.

Nonclinical Toxicology (13)
The [redacted] information was removed because we typically do not discuss the [redacted] in detail in the label.

Clinical Studies (14)

- The clinical studies section has been rewritten to describe the findings in the 12 week study. Fill in the Xs with the appropriate values.
- All data regarding [redacted] were removed to be consistent with current labels for asthma products in which [redacted] are not described in detail unless there was an appropriate pre-specified statistical analysis plan regarding the handling of the [redacted]
- Revise the figure in Section 14 as follows:
    - Remove the asterisks from the other timepoints (Day 15 and Day 57) because there was not an appropriate pre-specified statistical analysis plan for handing these additional timepoints.
    - Change [redacted] to [redacted] in the legend.
    - Include the number of subjects at each timepoint
    - Add trough to the vertical axis legend

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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Anthony Zeccola
5/1/2007 10:17:41 AM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-052

DISCIPLINE REVIEW LETTER

Critical Therapeutics, Inc.
60 Westview Street
Lexington, MA 02421

Attention: Roberta Tucker, R.Ph.

Dear Ms. Tucker:

Please refer to your July 31, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZYFLO XR™ (zileuton extended-release tablets).

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Regarding the drug substance

2. Regarding the drug product:
   a. Regarding the manufacturing procedure:
      (1)
      (2)
      (3)
      (4)
      (5)

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

testing is provide in the results for stability testing of the NDA Registration batches. In addition the various stability protocols in Sections P.8.1 and P.8.2 do not specify exactly which microbial tests will be performed.

(4) The proposed expiration date of 18 months is acceptable based on the results of the stability data for dissolution. Collection and analysis of additional data is recommended. Note that dissolution is a "pass/fail" test and is not suitable for linear regression analysis.

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

If you have any questions, call Anthony Zeccola, Regulatory Management Officer, at 301-796-1318.

Sincerely,

Blair A. Fraser, Ph.D.
Director
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
4/3/2007 04:55:40 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Michelle Safarik, DDMAC, HFD-042			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Anthony Zeccola, ODEII/DPAP	
DATE 3/22/07	IND NO.	NDA NO. 22-052	TYPE OF DOCUMENT N	DATE OF DOCUMENT 7/31/06
NAME OF DRUG Zyflo XR(zileuton extended-release tablets).	PRIORITY CONSIDERATION 1		CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE 4/13/07

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The draft label is located at: \\Cdsesub1\n22052\N_000\2006-07-20\spl\byflo.xml, as noted in the attached correspondence dated 2/15/07, they are changing the tradename to Zyflo XR. The attached correspondence contains the carton and container labeling for the new tradename

SIGNATURE OF REQUESTOR Anthony M. Zeccola	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

ORIGINAL

Critical Therapeutics, Inc.
[illegible] Street
Lexington, MA 02421

T: 781.402.5700
F: 781.402.5729
www.crtx.com

CRITICAL Therapeutics

NDA 22-052
ZYFLO XR™ (zileuton extended-release tablets)
Formerly (——— (zileuton) Controlled-Release Tablets)

February 8, 2007

Badrul A. Chowdhury, M.D., Ph.D., Director
Division of Pulmonary and Allergy Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

RE: AMENDMENT TO A PENDING APPLICATION
CHANGE IN PROPOSED NAME OF DRUG

Dear Dr. Chowdhury:

Reference is made to our original NDA 22-052 for the subject drug product submitted July 30, 2006.

In the original NDA, the drug product proposed name was " ——— " **(zileuton) Controlled-Release Tablets.**" Unfortunately, we have encountered trademark difficulties with the use of the name " ——— , therefore, we are now proposing a new trade and established name as follows:

"ZYFLO XR™ (zileuton extended-release tablets).

To that end, enclosed as an archival copy is revised draft labeling as follows:

Item 2:
Container labels (4 copies each)

- 20 tablets
- 120 tablets

Package Insert (4 copies each)

- A "track changes" version of the revised PI reflecting the name change as described above
- A "changes accepted" version of the revised PI

Structured Product Labeling (SPL) (1 copy)

- A diskette containing revised SPL (diskette mailed to "Electronic Data" at 5901-B Ammendale Road)

Please note that the SPL does not match the paper-copy package insert exactly. Due to the use of the FDA stylesheet and associated software, the first line of the SPL is incorrect: "ZYFLO XR™" displays as "Zyflo Xr". In addition, the SPL contains the description "multilayer tablet" in the header that we have been asked by the labeling reviewer to remove from our SPL in FDA's correspondence dated October 12, 2006; unfortunately, the SPL stylesheet does not allow for this to be deleted. Our SPL vendor has informed us that the FDA stylesheet and associated software will not allow us to correct these inconsistencies. Your assistance with this issue is requested.

If you have any additional questions, please contact me at (781) 402-5768 or Elizabeth Fenna at (781) 402-5762. Alternatively, you may send us a fax at (781) 402-5728.

Sincerely,

R Tucker

Roberta Tucker, R.Ph.
VP, Regulatory Affairs

7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Anthony Zeccola
3/22/2007 10:45:40 AM

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: March 22, 2007

To: Anthony Zeccola, Regulatory Project Manager
Division of Pulmonary and Allergy Products

From: Michelle Safarik, PA-C, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: NDA 22-052
DDMAC labeling comments for Zyflo XR (zileuton extended-release tablets)

Per your consult request dated March 22, 2007, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the proposed product labeling (PI) and proposed carton and container labeling for Zyflo XR (zileuton extended-release tablets (Zyflo XR), and we offer the following comments.

PI

Higlights

Indications and Usage

1. Is it appropriate to include Xyflo XR's drug class (leukotriene synthesis inhibitor) in an Indications and Usage section?

Dosage and Administration

1. [redacted]

   For consistency with the Dosage and Administration section of the proposed PI, we recommend adding the following phrase: "prior to initiation of [redacted] and periodically during treatment."

Contraindications

1. For consistency with the Contraindications section of the proposed PI, we recommend adding the following statement: [redacted]

Warnings and Precautions

1. For consistency with the Warnings and Precautions section of the proposed PI, we recommend adding the following statement: "Use with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease."

Use in Specific Populations

1. "Zyflo XR is contraindicated in patients with active liver disease."

   For consistency with the Use in Specific Populations – Hepatic Impairment section of the proposed PI, we recommend adding the following phrase: "or [redacted], persistent ALT elevations ≥3x ULN."

2. For consistency with the Use in Specific Populations – Pediatric Use section of the proposed PI, we recommend adding the following statement: "Safety and effectiveness of Xyflo XR in patients less than 12 years of age have not been established."

6.1 Clinical Studies Experience

1. [redacted]

   We recommend spelling out [redacted] to [redacted]

2. [redacted]

   Since this phrase discusses risk information, would it be possible to provide context for "most"?

7 Drug Interactions

1. We note that the Zyflo PI contains Warnings related to theophylline, warfarin, and propanolol, while the proposed Zyflo XR PI discusses these under "**7 Drug Interactions**" only. Is it appropriate to include theophylline, warfarin, and propanolol Warnings in the proposed Zylfo XR PI as well?

8.4 Pediatric Use

1. Is it appropriate to include a discussion of the safety and pharmacokinetics of zileuton IR in patients less than 12 years old when Zyflo XR's proposed indication is for those 12 years of age and older?

If so, DDMAC objects to phrases such as "[redacted]" "generally well tolerated," and "favorable safety profile/side effects" as these minimize the risks of drug therapy. Therefore, we recommend deletion of the phrase [redacted]

In addition, is it accurate to state that "The majority of adverse reactions were considered mild"?

11 Description

1. "...are triple-layer tablets comprised of a [redacted] layer, a middle (barrier) layer, and a [redacted] layer."

   "[redacted] and "[redacted] are promotional in tone; we recommend providing context or deleting.

12.1 Mechanism of Action

1. "Leukotrienes are [redacted] lipid mediators...."

   "[redacted] is promotional in tone; we recommend deletion.

14 Clinical Studies

1.

(emphasis added)

Since these terms and phrases discuss efficacy claims, would it be possible to provide context for each of them?

2. While we acknowledge that Table 1 and Figure 1 in the Zyflo PI present non-statistically significant findings, is it appropriate to do the same in Table 2 and Figure 2 of the proposed Zyflo XR PI?

3. "The results of both studies confirm that treatment with Zyflo XR, both as monotherapy and in conjunction with other asthma therapies, is efficacious in the prophylaxis and chronic treatment of asthma."

   This claim is repetitive with the graphs and text in this section of the proposed PI, unnecessary, and promotional in tone. Therefore, we recommend deletion.

17 Patient Counseling Information

1. We recommend revising " [redacted] and [redacted] throughout this section of the proposed PI to "health care provider" to reflect the variety of health care professionals (e.g. nurse practitioners, physician assistants) who may treat patients with asthma.

17.1 Information for Patients

1. [redacted]

   These claims are promotional in tone and inappropriate for patient counseling. Therefore, we recommend deletion.

2. "The most [redacted] side effect of Zyflo XR is potential elevation of liver enzymes...."

   We recommend revising " [redacted] to "serious" for clarity and consistency with the Zyflo PI.

17.2 FDA-Approved Patient Labeling

1. [redacted]

   This claim overstates the efficacy of Zyflo XR therapy by implying that all it takes to improve asthma is to block leukotrienes. Therefore, we recommend revising the above claim to read, "Blocking leukotriene production helps to improve asthma."

2. [redacted]

While accurate, this statement is an implied comparative claim suggesting superiority to steroids used to treat asthma. Therefore, we recommend deletion.

3. [redacted]

This statement is an unsubstantiated patient-reported outcome and quality-of-life claim. Therefore, though we acknowledge this claim in the Zyflo PI, it is extremely promotional in tone and we recommend deletion.

4. [redacted]

Is this statement accurate, particularly in light of the fact that according to the Adverse Reactions section of the proposed PI, the discontinuation rate for patients on Zyflo XR was 12.2%?

Carton and Container Labeling

1. [redacted]

Since the above statement from the proposed Dosage and Administration section of the proposed PI makes a representation (albeit accurate) about Xyflo XR, we recommend adding appropriate balancing risk information, or deleting the above statement.

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/s/

Michelle Safarik
3/22/2007 04:34:54 PM
DDMAC REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PREA WAIVER DENIED

IND 47, 561

Critical Therapeutics
60 Westview Street
Lexington, MA 02421

Attention: Roberta Tucker, R.Ph.
Vice President, Regulatory Affairs

Dear Ms. Tucker:

Please refer to your submission dated February 6, 2007, requesting a waiver under 505B(a)(4) of the Federal Food, Drug, and Cosmetic Act for pediatric studies for Zileuton Controlled-Release Tablets.

We have reviewed your submission and do not agree that a waiver of pediatric studies in patients up to 4 years of age is justified for Zileuton Controlled-Release Tablets for the prophylaxis and chronic treatment of asthma at this time.

We are denying this waiver for the following reason:

> The NDA for Zileuton Controlled-Release Tablets for patients 12 and older is currently under review. It is premature to make a final decision regarding the the waiver or deferral for patients 4 to 11 years of age.

Accordingly, a waiver for pediatric studies for this application is denied at this time. We recommend that you submit your pediatric drug development plan by 120 DAYS FROM DATE OF LETTER. Your pediatric drug development plan should address the following indication(s): Prophylaxis and chronic treatment of asthma.

If you have any questions, call Anthony M. Zeccola, Senior Regulatory Management Officer, at (301) 796-1318.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
3/5/2007 09:14:38 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447

FROM: Anthony Zeccola
Regulatory Management Officer
DPAP, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/5/07		22-052	N	July 31, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zyflo XR (zileuton extended-release tablets)	S	3	4/15/07

NAME OF FIRM: Critical Therapeutics, Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: A consult was previously submitted for [redacted]. On 2/15/07 we received correspondence from the Applicant stating that due to "trademark difficulties" they were changing the trade name of their product to Zyflo XR (see attachment).

PDUFA DATE: May 31, 2007
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-052
HFD-570/Division File
HFD-570/Zeccola/RPM
HFD-570/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Anthony Zeccola 301-796-1318	☒ DFS ONLY ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Memorandum of Telephone Facsimile Correspondence

Date: February 14, 2007

To: Roberta Tucker

Fax No.: 781-402-5728

From: Anthony M. Zeccola

Subject: FDA Request for Information
NDA 22-052 [redacted] (zileuton) Controlled-Release Tablets

Number of Pages: 3 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

See appended electronic signature page

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

We are reviewing your NDA, received July 31, 2006, and have the following information request.

1. You did not propose an expiration date; submit a proposal for an expiration date, updated stability data, and an analysis to support a proposed expiration date.

2. Provide statements from the suppliers of the packaging materials in contact with the drug product that the materials are acceptable for food contact per the appropriate sections of the CFR.

3. Provide full manufacturing procedure and specifications from Shasun for the manufacturing of the drug substance, including a master and executed batch record.

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/s/
Anthony Zeccola
2/14/2007 10:37:23 AM
CSO

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		**REQUEST FOR CONSULTATION**	
TO *(Division/Office)*: Division of Pulmonary Drug Products, Pharmacology/Toxicology Review Team		FROM: Arthur Shaw, Review Chemist, ONDQA/DPA1/Branch 2	
DATE December 21, 2006	NDA. 22052	TYPE OF DOCUMENT: Original NDA	DATE OF DOCUMENT July 31, 2006
NAME OF DRUG (zileuton) Extended Release Tablet	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE Febr1, 2007
NAME OF FIRM: Critical Therapeutics			

REASON FOR REQUEST: SAFETY ASSESSMENT

There are identified impurities in this NDA. The tablet contains 600 mg zileuton and is intended to be dosed twice a day.

Code	Name	Limit in NDA 20471 (%)	Proposed Limit in NDA 22052 (%)	Total Daily Intake (mg)	Structure

were present in Zyflo (zileuton) Tablets, NDA 20471. are present at slightly higher levels in . these were qualified for Zyflo in a toxicology study: "Three-Month Oral Safety Study of Abbott and Abbott (Zileuton Impurities) in Rats (Abbott Study No. TA96-382)." This report was submitted to the ZYFLO NDA (20-471) on May 1, 1997.

are present at levels less than or equal to the levels found in Zyflo ( ). One is a newly identified impurity.

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/s/

Arthur B. Shaw
12/21/2006 03:55:48 PM
CHEMIST
Tox consult for impurities

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447

FROM: Anthony Zeccola
Regulatory Management Officer
DPAP, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/3/06		22-052	N	July 31, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
— (zileuton) Controlled Release Tablets	S	3	4/15/07

NAME OF FIRM: Critical Therapeutics, Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

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IV. DRUG EXPERIENCE

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- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The Draft is located at: \\Cdsesub1\n22052\N_000\2006-07-20\spl\ — .ml. Please not that the CMC Reviewer has noted that the term "Controlled Released Tablets" is not an appropriate descriptor. This has not been conveyed to the Applicant, pending ODS comment.

PDUFA DATE: May 31, 2007
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-052
HFD-570/Division File
HFD-570/Zeccola/RPM
HFD-570/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Anthony Zeccola 301-796-1318	☒ DFS ONLY ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Anthony Zeccola
11/3/2006 02:40:07 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-052

Critical Therapeutics
60 Westview Street
Lexington, MA 02421

Attention: Roberta Tucker, R.Ph.
Vice President, Regulatory Affairs

Dear Ms. Tucker:

Please refer to your July 3, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ~~—~~ (zileuton) Controlled-Release Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 29, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. In the absence of direct pharmacokinetic comparisons of the proposed Formulation E21 to Abbott's Formulation H used in the Phase 3 safety and efficacy studies, the bridging between the two products will be a significant review issue.

2. Due to the multiplicity issues (e.g., no pre-specified primary efficacy variable or timepoint(s) for analysis), judging whether Study M95-337 demonstrated efficacy will be an important review issue. The protocol stated that trough FEV_1 would be analyzed using both mean changes from baseline and percent changes from baseline. However, the sample size discussion in the protocol states that sample size was chosen to detect a difference in percent change from baseline FEV_1 indicating that that may have been intended as the primary efficacy variable. Moreover there were multiple assessment times (Day 15, 29, 57 and 85) for each of these measures of FEV_1. You present in Appendix 2 of the study report a discussion of results of the use of the Hochberg procedure on the multiple assessment times for mean changes in FEV_1 and percent changes in FEV_1 treated individually. The applicability of this approach to this data, particularly since it is post-hoc, is unclear.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Clarify the following discrepancies in the data presented:

   a. In Volume 93, P 147, the Safety Conclusions report 7 hospitalizations due to asthma in the zileuton CR group compared to N=5 reported elsewhere in the results.

   b. Tables 14.2.B.11.4 and 14.2.C.6.4 report 2 versus 3 hospitalizations for Day 29.

2. Submit revised labeling incorporating the following comments:

   These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

   Highlights:

   - There is no space between Highlights of prescribing information and the Highlights limitation statement. Please correct.
     [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

   - For Initial U.S. Approval, this application is not approved. Delete '[redacted]'.
     [See 21 CFR 201.57(a)(3)]

   - The drug names must be followed by the drug's dosage form and route of administration. Please delete the word '[redacted]' [See 21 CFR 201.57(a)(2)]

   - The Dosage and Administration heading is listed twice. The third heading must read Dosage Forms and Strengths. Please correct.
     [See 21 CFR 201.56(d)(1) and 201.57(a)(8)]

   - Under Adverse Reactions, the term '[redacted]' is used instead of "adverse reactions." Refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise the Adverse Reactions heading in Highlights and the FPI accordingly.

   - There should be a space between the Use in Specific Populations information and the required patient counseling information statement.

   - A revision date must appear at the end of Highlights. For a new NDA this will be month/year of approval. [See 21 CFR 201.57(a)(15)]

Full Prescribing Information: Contents:

- Each subheading within a section must be indented and not bolded. Please correct. [See 21 CFR 201.57(d)(10)] In addition, refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format. There should be a space between numbers and headings and subheadings. This also applies to the FPI.

- Under Use in Specific Populations delete '[redacted]'. [See 21 CFR 201.57(b)]

- Under Clinical Pharmacology 12.1 must read Mechanism of Action, not Mechanism Of Action. [See 21 CFR 201.56(d)(1)]

- Under Nonclinical Toxicology 13.1 must read Carcinogenesis, Mutagenesis, Impairment of Fertility, not Carcinogenesis, Mutagenesis, Impairment Of Fertility. [See 21 CFR 201.56(d)(1)]

- Under Nonclinical Toxicology 13.2 is designated for Animal Toxicology and/or Pharmacology. [See 21 CFR 201.56(d)(1)] Therefore, 13.2 cannot be '[redacted]'. This must be designated as subsection 13.3. Use words to describe the content of a subsection. Avoid using the word '[redacted]'. This also applies to the FPI.

- The footnote *Sections or subsections omitted from the full prescribing information must be right justified. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

Full Prescribing Information (FPI):

- The preferred format for presenting the drug names is without all capital letters.

- The paragraphs throughout the FPI under the sections and subsections are not indented and aligned left. Indent each paragraph. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

- The preferred presentation of cross-references in the FPI is in all italics. For example, *[see Warnings and Precautions (5.2)]*, not [see *Warnings and Precautions (5.2)*]. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Please correct your cross-references throughout the labeling. [Implementation Guidance]

- Regarding Contraindications, "theoretical" possibilities must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction.
[See 21 CFR 201.57(c)(5)]

- Under Patient Counseling Information, any FDA-approved patient labeling must be referenced in this section. Add *[see 17.2 FDA-approved Patient Labeling]*. [See 21 CFR 201.57 (c)(18)]

- Delete "[redacted]" at the end of the labeling. The revision date at the end of Highlights replaces this information.

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

If you have any questions, call Anthony M. Zeccola, Senior Regulatory Management Officer, at (301) 796-1318.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
10/12/2006 10:46:29 AM

Date: September 28, 2006

From: Robin Anderson, RN, MBA
Label Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

Through: Laurie B. Burke, RPh, MPH
Director, SEALD

To: Anthony Zeccola
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: Proposed Labeling Format Review
NDA 22-052 — (zileuton) Controlled-Release Tablets

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant. Please contact me at 796-0534 with questions or concerns.

Comments to convey to the applicant:

These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Highlights:

- There is no space between Highlights of prescribing information and the Highlights limitation statement. Please correct.
  [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- For Initial U.S. Approval, this application is not approved. Delete "—".
  [See 21 CFR 201.57(a)(3)]

- The drug names must be followed by the drug's dosage form and route of administration. Please delete the word "—" [See 21 CFR 201.57(a)(2)]

- The Dosage and Administration heading is listed twice. The third heading must read Dosage Forms and Strengths. Please correct.
  [See 21 CFR 201.56(d)(1) and 201.57(a)(8)]

- Under Adverse Reactions, the term " [redacted] " is used instead of "adverse reactions." Refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise the Adverse Reactions heading in Highlights and the FPI accordingly.

- There should be a space between the Use in Specific Populations information and the required patient counseling information statement.

- A revision date must appear at the end of Highlights. For a new NDA this will be month/year of approval. [See 21 CFR 201.57(a)(15)]

Full Prescribing Information: Contents:

- Each subheading within a section must be indented and not bolded. Please correct. [See 21 CFR 201.57(d)(10)] In addition, refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format. There should be a space between numbers and headings and subheadings. This also applies to the FPI.

- Under Use in Specific Populations delete " [redacted] " [See 21 CFR 201.57(b)]

- Under Clinical Pharmacology 12.1 must read Mechanism of Action, not Mechanism Of Action. [See 21 CFR 201.56(d)(1)]

- Under Nonclinical Toxicology 13.1 must read Carcinogenesis, Mutagenesis, Impairment of Fertility, not Carcinogenesis, Mutagenesis, Impairment Of Fertility. [See 21 CFR 201.56(d)(1)]

- Under Nonclinical Toxicology 13.2 is designated for Animal Toxicology and/or Pharmacology. [See 21 CFR 201.56(d)(1)] Therefore, 13.2 cannot be "Other." This must be designated as subsection 13.3. Use words to describe the content of a subsection. Avoid using the word "Other." This also applies to the FPI.

- The footnote *Sections or subsections omitted from the full prescribing information must be right justified. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

Full Prescribing Information (FPI):

- The preferred format for presenting the drug names is without all capital letters.

- The paragraphs throughout the FPI under the sections and subsections are not indented and aligned left. Indent each paragraph. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

- The preferred presentation of cross-references in the FPI is in all italics. For example, *[see Warnings and Precautions (5.2)]*, not [see *Warnings and Precautions (5.2)*]. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Please correct your cross-references throughout the labeling. [Implementation Guidance]

- Regarding Contraindications, "theoretical" possibilities must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction.
[See 21 CFR 201.57(c)(5)]

- Under Patient Counseling Information, any FDA-approved patient labeling must be referenced in this section. Add *[see 17.2 FDA-approved Patient Labeling]*.
[See 21 CFR 201.57 (c)(18)]

- Delete " [redacted] at the end of the labeling. The revision date at the end of Highlights replaces this information.

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

/s/

Robin E Anderson
9/29/2006 09:11:28 AM
CSO

Laurie Burke
10/2/2006 06:49:51 PM
INTERDISCIPLINARY

Critical Therapeutics, Inc.
60 Westview Street
Lexington, MA 02421

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CRITICAL Therapeutics

July 30, 2006

Badrul A. Chowdhury, M.D., Ph.D., Director
Division of Pulmonary and Allergy Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

Re: ORIGINAL NEW DRUG APPLICATION: NDA 22-052
[redacted] (zileuton) Controlled-Release Tablets

Dear Dr. Chowdhury:

In accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and Title 21 Part 314.50 of the Code of Federal Regulations, Critical Therapeutics Inc. herewith submits a New Drug Application for [redacted] (zileuton) Controlled-Release Tablets, NDA 22-052, for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older. The dosage regimen for [redacted] is two 600-mg tablets twice a day, within one hour of a meal, for a total daily dose of 2400 mg.

The immediate-release formulation of zileuton, Zyflo® (zileuton tablets), NDA 20-471, was approved December 9, 1996 for the same indication and is currently on the market at a dosage regimen of one 600 mg tablet four times a day, with or without food.

Th[redacted] NDA contains 314 volumes. Please refer to the Reviewer's Guide in Volume 1 for further details. Cross-reference is made to the approved Zyflo NDA where pertinent. The NDA is primarily a paper NDA. Case report forms for subjects/patients who died or discontinued prematurely from the studies due to adverse events (AEs) are provided in PDF format per the Division's request. The proposed Package Insert is provided in Structured Product Labeling (SPL) format. In addition, pertinent SAS datasets and related SAS programs for the primary efficacy analyses, selected secondary efficacy analyses, and integrated adverse event analyses are provided on a compact disk.

A signed FDA Form 356h, a User Fee Cover Sheet, a debarment certification, a copy of the letter that accompanies the field copy of the CMC and Methods Validation section of the NDA, and patent information follow this letter. An introduction to the format, content and organization is provided for use as a Reviewer's Guide.

Should you have any questions concerning this NDA, please contact the undersigned at telephone number (781) 402-5768 or Elizabeth Fenna at (781) 402-5762. Our fax number is (781) 402-5728.

Sincerely,

Roberta Tucker

Roberta Tucker, RPh
VP, Regulatory Affairs
Critical Therapeutics Inc.

Copy: Anthony Zeccola, Project Manager, Division of Pulmonary and Allergy Drug Products

ACTION PACKAGE CHECKLIST

Application Information		
NDA # 22-052	NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Zyflo XR Established Name: Zileuton Extended Release Dosage Form: Tablets		Applicant: Critical Therapeutics, Inc.
RPM: Zeccola		Division: Pulmonary and Allergy Products / Phone # 301-796-1318

NDAs: NDA Application Type: X 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	May 31, 2007
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☐ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

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

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes **X NO**
• This application is on the AIP	☐ Yes **X NO**
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes **X NO**
• Press Office notified of action	☐ Yes **X NO**
• Indicate what types (if any) of information dissemination are anticipated	**X None** ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	**X Included**
• Is approval of this application blocked by any type of exclusivity?	**X NO** ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	**X Verified** ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

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

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

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

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

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

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

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

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

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

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	5/30/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	5/30/07
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	**5/14/07**
• Original applicant-proposed labeling	**7/30/06**
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	**5/14/07**
• Original applicant-proposed labeling	**7/30/06**
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	5/30/07
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☐ DMETS ☐ DSRCS X **DDMAC** 3/22/07 ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	5/17/07
NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	**X Verified, statement is acceptable**
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 4/27/05
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	**3/26/07** CTL
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☐ None **Pharm/Tox** 2/22/07, 3/6/07
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	3/26/07
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	3/14/07 ☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 3/25/07 X **Acceptable** ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☑ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	3/29/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	**X None**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**4/22/07**
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	**4/22/07 Page 16**
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	**X None**
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	**X Not needed**
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	**4/22/07 Page 43**
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	**4/22/07 Page 47**
Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	**X Not needed**
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None **12/6/06**
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None **3/26/07**

Appendix A to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).

(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.

(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).

(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.

(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Memorandum of Telephone Facsimile Correspondence

Date: April 27, 2005

To: Roberta Tucker, R.Ph.

Fax No.: 781-402-5728

From: Anthony M. Zeccola

Subject: FDA Response to Pre-NDA Questions dated March 22, 2005
Critical Therapeutics, Inc., IND 47, 561 – Zileuton Controlled-Release Tablets.

Number of Pages: 13 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

(See appended electronic signature page)

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

Attached are the FDA responses to the questions (in **bold**) in your meeting package regarding Zileuton Controlled-Release Tablets. You have the option of canceling our meetings scheduled for May 2, 2005, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback should be submitted as a new meeting request. Please let me know as soon as possible if you would like to cancel the meeting or change it to a teleconference.

1. **The submission, except for the CMC section, will be in an NDA format as opposed to the CTD format...The CMC section will be in the CTD format. Is this acceptable to the Division?**

   Yes.

2. **The submission will be a paper NDA as opposed to an electronic submission...Is this acceptable to the Division?**

   Yes.

3. **Table of Adverse Events: We plan to provide data from the two pivotal studies using the full analysis set as opposed to the restricted analysis set. Is this acceptable to the Division?**

   This will be determined after reviewing results of the analyses. In the NDA, justify the analysis set you use for the Adverse Events Table(s) in the package insert. See the response to question 16.

   In addition, provide table(s) in the Integrated Summary of Safety to support the Adverse Events Table(s) you intend to include in labeling; i.e., if adverse events occurring at ≥2% frequency are displayed in the package insert, an analogous table should be found in the ISS.

4. **We propose that the drug substance section of the CR tablet NDA be provided as a cross-reference to the drug substance section of the Critical Therapeutics' sNDA for Zyflo (zileuton) Tablets (to be submitted to NDA 20-471 end of March 2005), since information for the drug substance sections of both submissions will be identical. Is this acceptable?**

   This approach is reasonable. Please include references and date of submission in the NDA.

3 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

13. **The Pharmacology and Toxicology sections of the CR NDA will consist of a cross-reference to the approval of NDA 20-471 and sNDA planned for submission March 2005. Additional toxicology studies were conducted to qualify t — impurities that may be present in the drug substance manufactured with the — process. Final study reports will be submitted in March 2005 sNDA to NDA 20-471 (Zyflo® IR tablets). In the CR NDA, we will cross-reference the Zyflo® UR sNDA for the three toxicology studies described above. Additional, toxicology studies have been performed to qualify a new degradant [redacted] that may be present in the CR tablets ([redacted] the final study reports will be included in the NDA for zileuton CR tablets. Is this approach acceptable to the Division?**

Submit full reports of all relevant qualification studies to this NDA

Any new impurities/degradants require qualification at [redacted] (drug substance) and [redacted] (drug product)

For other impurities/degradants increased above previous specifications, qualification is required

14. **The first six biopharmaceutics studies were conducted by Abbott to evaluate several prototypes of zileuton CR formulation prior to selecting a formulation for development. These exploratory studies were not performed under IND 47, 561. We propose to submit the clinical reports without appendices and data listings for these six exploratory studies. Case report forms for drop-outs and deaths due to adverse events will also be submitted. The safety data from these Phase 1 studies will be integrated into the ISS with all the other Phase 1 studies. Is this acceptable to the Division.**

The approach is acceptable, but do not combine results from the exploratory formulations with those from the final formulation. Results from all exploratory formulations may be combined, but the Division wants to be able to separate them from the results from formulation(s) closest to the to-be-marketed.

It is acceptable per Clinical Pharmacology/Biopharmaceutics standpoint

15a. **For the purpose of historical comparison, CRTX proposes the following criteria be used to compare the pharmacokinetic parameters obtained from the CRTX**

definitive bioavailability study: mean Cmax and AUC values obtained from CRTX zileuton CR data will be considered similar to those from Abbott zileuton CR data if 95% confidence intervals around the ratio of the mean values of the two formulations (Cmax CRTX CR/Cmax Abbott CR and AUC CRTX CR/AUC Abbott CR) contain the value of 1. Tmax values will be compared descriptively between the two formulations. A literature search has identified a precedent for this methodology, where 95% confidence intervals were constructed for the ratio of pharmacokinetic parameters from two separate studies and the reference group was a historical control. This is the methodology that was used for assessments of the pharmacokinetics of esomeprazole (Nexium®) in the elderly and appears to be the basis for statements regarding geriatric populations in the package insert. Does the Division concur with the criteria proposed? Reference is made to the proposed design of the definitive bioavailability study submitted in the pre-NDA meeting briefing package on page 042. CRTX is proposing to conduct a single-dose bioavailability study Comparing the 600 mg zileuton CR tablet (S6 formulation) manufactured at [redacted] to the reference zileuton IR (Zyflo) tablet manufactured at Abbott. The study design would be similar to the Food Effect Study (M96-556) conducted by Abbott, in which the CR and IR formulations were administered under fasting and non-fasting conditions. In Question 15, we proposed that the comparison of pharmacokinetic parameters, Tmax, Cmax and AUC∞ for zileuton CR versus zileuton IR be based on non-fasted rather than fasted conditions. Considering that (1) the intended use of zileuton CR is for the chronic treatment of asthma, (2) all Phase III studies were conducted following administration of zileuton CR every 12 hours after meals, and (3) only historical comparison to the zileuton CR formulation from Abbott is feasible, CRTX is now proposing to conduct a multiple-dose bioavailability study comparing the 600 mg CRTX zileuton CR tablet manufactured at [redacted] to the reference zileuton IR (Zyflo) tablet manufactured at Abbott. The study design would be similar to the definitive multiple-dose bioavailability study conducted by Abbott (M95-264), in which the CR and IR formulations were administered at their intended dosage regimen (ql2h for CR or q6h for IR) for 6 days to reach steady state. The study would be designed as a two-period, open-label, non-fasting, randomized, cross-over study in 24 healthy volunteers, with 10 days wash-out between periods. Pharmacokinetic parameters, Tmax, Cmax, Cmin and AUC0-24, would be determined from data collected on Day 6 at steady state. For the purpose of historical comparison to zileuton CR manufactured by Abbott, results of the definitive BA study will be interpreted in the context of the results reported by Abbott from the multiple-dose bioavailability study (M95-264). Similar to what was described above, mean Cmax, Cmin and AUC0-24 steady state values of zileuton CR tablets from the CRTX bioavailability study will be considered similar to those obtained from Abbott zilcuton CR data if 95% confidence intervals around the ratios of the mean values of each PK parameter contain 1. Tmax values will be compared descriptively between the two formulations. Does the Division concur?

Your approach is acceptable, however, if you plan to market formulation E21, the following is recommended.

- *Single dose study:*
  - *Design: Include 4 arms*
    - *S6 formulation (fasted condition)*
    - *E21 formulation (fasted condition)*
    - *E21 formulation (non-fasted condition)*
    - *IR formulation (non-fasted condition)*
  - *BE comparisons:*
    - *E21 fasted vs. S6 fasted*
    - *E21 fed vs. E21 fasted*
    - *E21 fed vs. IR non-fasted*
- *Multiple-dose study: Include 2-arms*
  - *E21 formulation (non-fasted condition)*
  - *IR formulation (non-fasted condition)*

Regarding the proposed criteria for cross-study comparison:

- *This is a review issue*
- *Report both 90% and 95% CI*
- *We will consider the impact of difference in BA from the recommended single and multiple-dose studies to those data from M95-556 and M96-264 in terms of safety and efficacy that were obtained from the two Phase III studies (M95-337, M96-464)*

16. Does the Agency concur with the definition of the analysis sets and our proposal to provide amended reports?

No. Submit the following three analysis sets:

Full Analysis Set: all patients except those from Edwards' center

Restricted Analysis Set: additionally excludes patients from the 15 sites unavailable for audit plus the patient who participated in both studies

Per Contract Analysis Set: additionally excludes patients from Fiddes' site. Also, provide justification in the NDA for excluding Fiddes site on the basis of contractual violation.

The data from Edwards' center should be available in the event it is requested. Clearly indicate in the NDA which analysis is considered primary and justify it. Will study reports be amended in any other manner? If yes, how?

17. **In reviewing the reports from Abbott, we have found that Abbott tested treatment effects using ANOVA models which had an investigator-treatment interaction term present, hence confounding the treatment-effect inferential tests. For the amended study reports and the ISE, we propose to re-perform the analyses for the Phase III studies using the appropriate statistical methodology. Treatment effects will be tested with only treatment and investigator main effects in the model. Additionally, a model with investigator, treatment, and investigator-treatment interaction will be fit to investigate whether the treatment effect is homogeneous across investigative sites. It should be noted that in the present of true heterogeneity across sites, the interpretation of the main treatment effect is controversial. For selected variables of particular importance, if investigator-treatment interaction is significant (using a = 0.100), then by-site analyses will be conducted. This approach is consistent with that recommended in ICH E9. This model will be applied to all analysis sets in the amended reports. Does the Agency concur with this approach?**

We agree with the specified analysis model to include treatment and center without the treatment by center interaction and that the interaction effect is to be explored.

18. **We plan to provide an update of the zileuton IR post-marketing events in Item 8F, Commercial Marketing Experience, of the NDA. We plan to include an update from July 29, 2004, the date we assumed ownership of the NDA from Abbott. Is this approach acceptable to the Division?**

The description of the Commercial Marketing Experience of zileuton IR should include summaries of all the Abbott IR post-marketing reports, updated by CRTX through the most recent date for which data can feasibly be included in the NDA.

[Questions 19 and 22 are answered together as follows]

19. **A brief summary of all ongoing studies with zileuton CR for all other indications will be provided. Is this approach acceptable to the Division?**

22.

20. The three analysis sets (full set, restricted set, and per protocol set) defined for the efficacy analyses of the individual study reports will be used to evaluate efficacy of zileuton CR in the ISE. Is the content and format of the ISE acceptable?

The format and content appear to be acceptable.

Support for the efficacy and safety of CRTX zileuton CR, however, rests in the link(s) that must be made to the Abbott IR and Abbott CR data. If those links break down for any reason, the Phase 3 clinical evidence for efficacy and safety derived from the Abbott CR drug product would be vulnerable.

The original Abbott CR program rested on demonstration of similar systemic exposure between the CR and IR drug products in addition to the two clinical studies. The PK data provided in your submission now make it apparent that systemic exposure from the CR (demonstrated in AUC data) is markedly lower than from the IR drug product. Knowing this, the NDA should include justification that the Phase 3 clinical data for Abbott CR can stand independently of IR to support the efficacy of your drug product.

21. In the ISS we plan to present integrated safety data from the Phase I studies (all but one were single-dose studies), and integrated data from the two Phase III studies. For the Phase III studies, we plan to analyze the full analysis set and the restricted analysis set. The statistical analyses plan is included in Appendix 5 of this Briefing Package. Is the content and format of the ISS acceptable?

The proposed content and format of the ISS is generally acceptable, with the following additional recommendations.

You have stated that you plan to use MedDRA for reporting of adverse events for all clinical studies. If MedDRA terminology was not used in the original study reports, the ISS will need to specify how the adverse events were recoded.

In the ISS, provide a summary and integrated analyses of all hepatocellular and hepatobiliary events from the studies, including laboratory findings from the MedDRA "Investigations" SOC to allow an overview of the hepatic-related safety of the drug.

Specify each of the "Other" reasons for patients discontinuing from the studies, rather than combine them all.

Include race in the subgroup analyses of laboratory findings and vital signs, in addition to age and gender.

Refer also to the responses to questions 3 and 14.

23. Is the outline of the analyses we plan to submit to support a risk management plan acceptable to the Division?

Yes.

24. Per the regulations, we plan to submit in this NDA case report forms for all deaths and drop-outs due to adverse events including placebo and reference drugs for all studies conducted with zileuton CR for asthma. Is this acceptable to the Division?

Yes.

26. In addition [to CMC information], the safety update will include the status of any ongoing clinical studies being conducted with the CR formulation for asthma as well as CRFs for any deaths or drop-outs due to AEs from these studies. Is this acceptable to the Division?

As per 21 CFR 314.50 (d)(5)(vi)(b), the 4-month safety update should include the CRFs and status of clinical studies, but should also include any information from any source about the safety of the product.

27. CRFs: Does the Division prefer to receive PDF files of the CRFs, or paper copies, or both?

PDF files are preferred.

28. Labeling: We plan to submit draft facsimile labeling as well as the container labels in PDF and the package insert in Word on a CD. Is this acceptable?

The proposal is acceptable but we encourage you to consider using the Structured Product Labeling (SPL) format instead.

29. Statistical Data: Electronic SAS datasets for the primary and secondary efficacy variables (FEV1 and PEFR) will be submitted and with the integrated adverse event dataset for the Phase I studies and an integrated adverse event dataset for the Phase III studies. Is this acceptable?

Submitting the SAS datasets on the primary and secondary efficacy endpoints and the safety endpoints for the two phase III trials is acceptable.

Additional CMC Comments

Qualify all impurities in the drug substance above [redacted] and drug product above [redacted] Refer to current ICH guidance documents (Q3A and Q3B(R)).

If these impurities and degradants are already qualified, provide references to the studies and the results as part of the NDA submission.

Additional General Comment

Refer to the new FDA Guidance for Review Staff and Industry, "Good Review Management Principles and Practices for PDUFA Products." The Guidance will inform your expectations and responsibilities during review of the NDA. The Division will adhere to the Guidance unless communicated otherwise to you.

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/s/

Anthony Zeccola
4/27/05 08:23:49 AM
CSO