CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-052

CHEMISTRY REVIEW(S)

Zyflo XR
(zileuton)
Extended Release Tablets

NDA 22-052

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

Applicant: Critical Therapeutics
60 Westview Street
Lexington, MA 02421 USA

Indication: Chronic treatment of asthma in adults and children 12 years of age and older.

Presentation: Extended Release (XR) Tablets, 600 mg strength, triple-layer tablets comprised of a fast-release layer, a middle (barrier) layer, and a slow-release layer. Tablets are oblong, film-coated tablets with one red layer between two white layers, debossed on fast-release side with "CT2" and packaged, 120 count, in a white HDPE bottle with PP CR closure with a [redacted] and a cotton coiler.

EER Status: Acceptable 10-APR-2007

Consults:

	Microbiology	Acceptable 14-MAR-2007
	Pharm/Tox	Acceptable 22-FEB-2007

EA – Categorical exclusion granted under 21 CFR §25.31(b).

Original Submission: 24-JUL-2006

Post-Approval Agreements:

The applicant has agreed to submit the following additional information:

- Additional information to support the methods validation.
- Data from ten consecutive batches to support discontinuation of in-process [redacted] testing.
- Stability data for the first [redacted] months of stability data on three commercial-scale validation batches.
- Data to support the holding time for the [redacted]

Drug Substance:

Zileuton is an orally active inhibitor of 5-lipoxygenase, the enzyme that catalyzes the formation of leukotrienes from arachidonic acid. The drug substance has the chemical name (±)-1-(1-Benzo(b)thien-2-ylethyl)-1-hydroxyurea, an empirical formula of $C_{11}H_{12}N_2O_2S$, and a molecular weight of 236.29 g/mol. It is a racemic mixture of R(+) and S(-) enantiomers. Zileuton is a white, crystalline powder that is soluble in methanol and ethanol, slightly soluble in acetonitrile,

and practically insoluble in water and hexane. [redacted]

[redacted]. The drug substance has been approved for use in Zyflo (zileuton) Tablets under NDA 20-471.

The proposed release specifications include: [redacted]

The bulk drug substance is packaged in a [redacted] The bulk drug substance was shown to be stable for a [redacted]

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product, ZYFLO XR (zileuton), is a coated, three-layer extended release tablet, 600 mg strength, comprised of a fast-release layer, a middle (barrier) layer, and a slow-release layer. Tablets are oblong, film-coated tablets with one red layer between two white layers, debossed on fast-release side with "CT2".

The "fast-release" (FR) layer disintegrates within [redacted], and contains [redacted] of the drug. The middle layer is a [redacted] that slows the release of drug substance **from the "slow-release" (SR) layer. The SR layer contains the remaining [redacted] of the** drug.

The overall composition of the 600 mg strength tablet is Zileuton (600 mg) and the following inactive ingredients: crospovidone NF [redacted], ferric oxide NF [redacted], glyceryl behenate NF [redacted], hydroxypropyl cellulose NF [redacted], hypromellose USP [redacted], magnesium stearate NF [redacted], mannitol USP [redacted], microcrystalline cellulose NF [redacted], povidone USP [redacted], pregelatinized starch NF [redacted], propylene glycol USP [redacted], sodium starch glycolate NF [redacted], and talc USP [redacted] for a total tablet weight of [redacted] mg.

Specifications for the drug product include: [redacted]. The impurities and their levels in the drug product have been qualified. All test methods have been appropriately validated for their intended purpose. The reference standard is zileuton USP RS or a suitable secondary standard. These are the same reference standards as those used for NDA 20-471 SCM-011.

Stability data were provided to support the proposed expiration dating of 18 months at room temperature, between 20 and 25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F), for the drug product packaged in HDPE bottles with [redacted] and protected from light.

Conclusion: Drug product is satisfactory.

Additional Items:

The applicant's proposal to eliminate testing for [redacted] and [redacted] in the finished product specifications after suitable data has been collected is acceptable. Approval of these changes will depend upon submission and review of the appropriate data and information.

The applicant's proposal to replace testing [redacted] **with** testing Content Uniformity by Tablet Weight is acceptable. Approval of this change will depend upon submission and review of the appropriate data and information.

The applicant's proposal to eliminate two in-process controls [redacted] is acceptable. Approval of these changes will depend upon submission and review of the appropriate data and information.

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

The analytical methods used in testing are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**, pending agreement on product labeling.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
4/28/2007 08:16:32 PM
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Chemistry Review Cover Sheet

NDA 22-052
Zyflo XR™ (zileuton) Extended Release Tablets
Arthur B. Shaw, Ph.D.
ONDQA/DPA1

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Chemistry Review Data Sheet

1. NDA 22052
2. REVIEW #2
3. REVIEW DATE: April 27, 2007
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

Submissions Reviewed	Document Date
Original	24-Jul-2006
Labeling Amendment	08-Feb-2007
Amendment	23-Feb-2007
Amendment	26-Feb-2007
Chem Review #1	26-Mar-2007
Discipline Review Letter	03-Apr-2007

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date
Amendment	12-Apr-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Critical Therapeutics
Address: 60 Westview Street
Lexington, MA 02421 USA
Representative: Roberta Tucker

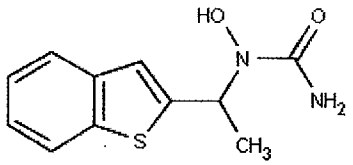
8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Zyflo XR
Non-Proprietary Name (USAN): zileuton
Chem. Type/Submission Priority

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A.
10. PHARMACOL. CATEGORY/INDICATION: 5-lipoxygenase inhibitor/treatment of asthma
11. DOSAGE FORM: Extended release tablet
12. STRENGTH/POTENCY: 600 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X__Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-1-(1-Benzo(b)thien-2-ylethyl)-1-hydroxyurea



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

The packaging DMFs did not need to be reviewed because there is sufficient information in the NDA. See "Container-Closure" section below.\

DMF	HOLDER	ITEM REFERENCED

B. Other Documents: Both applications belong to the applicant

DOCUMENT	APPLICATION NUMBER	DESCRIPTION	LOA Date
IND	47561	Zileuton Controlled Release Tablets	20-Apr-2005
NDA	20471	Zileuton Tablets (Immediate release)	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE of Original Consult Review	REVIEWER
Pharm/Tox	Recommended tightening acceptance criteria for — impurities. Acceptance criteria tightened by applicant in response to DR letter. **ACCEPTABLE**	22-Feb-2007	Jean Wu
Microbiology	Approvable pending submission of risk management program or adding test for microbial limits. Microbial limit test added to specification by applicant in response to DR letter **ACCEPTABLE**	14-Mar-2007	John Metcalfe
Inspections	**ACCEPTABLE**	10-Ap-2007	

The Chemistry Review for NDA 22052

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be **APPROVED** in terms of Chemistry, Manufacturing, and Controls.

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

The applicant has agreed to submit the following additional information:

1. Additional information to support the methods validation (CBE-0).
2. Data from [redacted] consecutive batches to support discontinuation of in-process [redacted] testing (Prior Approval)
3. Stability data for the first [redacted] months of stability data on three commercial-scale validation batches. (CBE-0).
4. Data to support the holding time for the [redacted]

Extension of the expiration date via Annual Report will be based on full stability for the first three commercial batches rather than the stability batches in the application.

There are two comments for future reviewers to alert them to the need for data to support possible changes in the excipient ranges and dissolution testing.

II. Summary of Chemistry Assessments

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

1. Drug Substance:

The drug substance is the same as the drug substance used in approved Zyflo (zileuton) Tablets (NDA 20-471). Most of the information regarding the drug substance was provided in NDA 20-471 Supplement 11, approved in 1995. Zileuton is a white powder, [redacted]

[redacted] The drug is synthesized as a racemate and has no detectable optical rotation. [redacted]

2. Drug Product

Zyflo XR is a coated three-layer extended release tablet intended to permit twice daily dosing compared with the q.i.d. schedule for the approved immediate release (IR) product, Zyflo. [redacted] The first layer is a

"fast-release" (FR) layer which disintegrates within [redacted] and contains [redacted] of the drug. The second layer is a [redacted] that slows the release of drug substance from the third layer, which is a "slow-release" (SR) layer. The SR layer contains the remaining [redacted] of the drug. The formulation was initially developed by Abbott Laboratories, based on a formulation developed by Jago Pharmaceuticals (now SkyePharma Pharmaceuticals.) Abbott performed the pivotal clinical trials using "Formulation H" In vitro dissolution studies showed that this formulation released [redacted] of the drug at six hours using a paddle speed of 100 rpm. The FR layer [redacted] as the approved IR tablet. [redacted] did further development work for the applicant, Critical Therapeutics (CRTX), and renamed the Abbott formulation "S6." [redacted] then developed a different formulation (E21), which differs from Abbott's formulation [redacted] CRTX modified the dissolution assay to use a paddle speed of 75 rpm. The dissolution at 6 hours was [redacted]. This formulation was used in bioavailability studies comparing the drug product with the approved IR tablet. No tablets manufactured by Abbott used in the previous pivotal clinical trials were available for direct comparison.

[redacted]

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The drug product contains a number of impurities also present in Zyflo IR tablets. One of these, [redacted] (Code name [redacted]) is present with a limit of [redacted]% in Zyflo IR. The original proposed specification for this impurity in Zyflo XR was [redacted] Toxicology studies in rats support a limit of [redacted] for dosing in humans. The applicant has tightened the acceptance criteria t[redacted]

Another impurity, [redacted], was present at less tha[redacted]% in Zyflo IR tablets as an "unspecified" impurity and is considered a "new" impurity by the applicant. The proposed specification for this impurity in Zyflo XR was [redacted] Toxicology studies in rats support a limit of [redacted] for dosing in humans. The applicant has tightened the acceptance criteria t[redacted]

Batch release data support a the new acceptance criteria for the impurities The stability data provided for 12 months at 25oC/60%RH support the proposed expiration date of 18 months.

The in vitro dissolution data shows that the amount dissolved at 6 hours increases with increasing storage time and temperature. Since dissolution is a pass/fail test the results cannot be extrapolated more than six months beyond the recorded data.

The applicant's proposal to eliminate testing for [redacted] in the finished product specifications after suitable data has been collected. (Sunset Provisions) is **ACCEPTABLE.** The applicant's proposal to replace testing [redacted] with testing Content Uniformity by Tablet Weight as a similar Sunset Provision is also **ACCEPTABLE**

The applicant's proposal to replace testing for re[redacted] as an in-process control with a test for [redacted] is **ACCEPTABLE**

The applicant's proposal to eliminate [redacted] cannot be implemented until sufficient data is collected at the commercial scale. This change will be filed as a Prior Approval Supplement.

The drug product manufacturing process has been scaled up but attempts to scale up to commercial batch size failed.

A Categorical Exclusion from the necessity to file an Environmental Assesment has been granted.

Inspection of all sites is **ACCEPTABLE**

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

The product is intended for oral dosing two times a day for the treatment of asthma.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance is the same as in the approved NDA 20471. The drug product is adequately controlled during manufacturing up to a scale of [redacted] tablets. The tests and specifications are adequate to control the performance of the drug product. The CGMP status of the facilities is acceptable

Administrative **Signed off in DFS**

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Arthur B. Shaw
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Chem Review #2

Blair Fraser
4/27/2007 07:43:39 PM
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Chemistry Review Cover Sheet

NDA 22-052
Zyflo XR™ (zileuton) Extended Release Tablets
Arthur B. Shaw, Ph.D.
ONDQA/DPA1

Chemistry Review Data Sheet

1. NDA 22052
2. REVIEW #1
3. REVIEW DATE: March 25, 2007
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date
Original	24-Jul-2006
Labeling Amendment	08-Feb-2007
Amendment	23-Feb-2007
Amendment	26-Feb-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Critical Therapeutics
Address: 60 Westview Street
Lexington, MA 02421 USA
Representative: Roberta Tucker

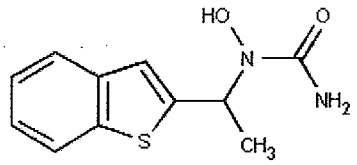
8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Zyflo XR
Non-Proprietary Name (USAN): zileuton
Chem. Type/Submission Priority

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A.
10. PHARMACOL. CATEGORY/INDICATION: 5-lipoxygenase inhibitor/treatment of asthma
11. DOSAGE FORM: Extended release tablet
12. STRENGTH/POTENCY: 600 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X__Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-1-(1-Benzo(b)thien-2-ylethyl)-1-hydroxyurea



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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DMF	HOLDER	ITEM REFERENCED

B. Other Documents: Both applications belong to the applicant

DOCUMENT	APPLICATION NUMBER	DESCRIPTION	LOA Date
IND	47561	Zileuton Controlled Release Tablets	20-Apr-2005
NDA	20471	Zileuton Tablets (Immediate release)	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Pharm/Tox	Impurity levels assessed. Recommended tightening acceptance criteria for ~~—~~ of them See review	22-Feb-2007	Jean Wu
Microbiology	Approvable pending submission of risk management program	14-Mar-2007	John Metcalfe
Inspections	Two sites not complete	25-Mar-2007	

The Chemistry Review for NDA 22052

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable in terms of Chemistry, Manufacturing, and Controls. See list of Deficiencies and Comments

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

N/A

II. Summary of Chemistry Assessments

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

1. Drug Substance:

The drug substance is the same as the drug substance used in approved Zyflo (zileuton) Tablets (NDA 20-471). Most of the information regarding the drug substance was provided in NDA 20-471 Supplement 11, approved in 1995. Zileuton is a white powder.

. The drug is synthesized as a racemate and has no detectable optical rotation.

The , procedure for the drug substance is tightly controlled in order to ensure reproducible manufacturing of the drug product.

2. Drug Product

Zyflo XR is a coated three-layer extended release tablet intended to permit twice daily dosing compared with the q.i.d. schedule for the approved immediate release (IR) product, Zyflo.

The first layer is a "fast-release" (FR) layer which disintegrates within and contains of the drug. The second layer is a ; that slows the release of drug substance from the third layer, which is a "slow-release" (SR) layer. The SR layer contains the remaining of the drug. The formulation was initially developed by Abbott Laboratories, based on a formulation developed by Jago Pharmaceuticals (now SkyePharma Pharmaceuticals.) Abbott performed the pivotal clinical trials using "Formulation H." In vitro dissolution studies showed that this formulation released of the drug at six hours using a paddle speed of 100 rpm. The FR layer the approved IR tablet. d further development work for the applicant, Critical Therapeutics (CRTX) and renamed the Abbott formulation "S6." en developed a different formulation (E21), which differs from Abbott's formulation o

[redacted]. CRTX modified the dissolution assay to use a paddle speed of 75 rpm. The dissolution at 6 hours was [redacted]. This formulation was used in bioavailability studies comparing the drug product with the approved IR tablet. No tablets manufactured by Abbott used in the previous pivotal clinical trials were available for direct comparison.

[redacted]

The drug product contains a number of impurities also present in Zyflo IR tablets. One of these, [redacted] is present with a limit of [redacted] in Zyflo IR. The proposed specification for this impurity in Zyflo XR is [redacted] Toxicology studies in rats support a limit of [redacted] for dosing in humans.

Another impurity, [redacted] was present at less than [redacted] in Zyflo IR tablets as an "unspecified" impurity and is considered a "new" impurity by the applicant. The proposed specification for this impurity in Zyflo XR is [redacted] Toxicology studies in rats support a limit of [redacted] for dosing in humans.

Batch release data support a limit of [redacted] for [redacted] and [redacted] for [redacted] The stability data provided for 12 months at 25oC/60%RH support a these limits at the proposed expiration date of 18 months.

The in vitro dissolution data shows that the amount dissolved at 6 hours increases with increasing storage time and temperature. Since dissolution is a pass/fail test the results cannot be extrapolated more than six months beyond the recorded data.

The applicant has proposed not testing for "Total Aerobic Microbial Count" based on their argument that the low water activity in the tablets inhibits bacterial growth. Data reported for the stability batches shows <10cfu/g. A consult review from Microbiology recommends that the applicant submit the results of this test from the first [redacted] batches post-approval followed by a supplement to [redacted]

The applicant has proposed that a number of tests in the finished product specifications be eliminated after suitable data has been collected. (Sunset Provisions) Three of these tests, [redacted], and [redacted], are acceptable to be eliminated after suitable data is collected. The finished product test for [redacted] is proposed to be replaced by Content Uniformity by Tablet Weight. The acceptability of this proposal cannot be assessed because the applicant did not provide the results of testing for content uniformity in the application.

Two [redacted] are also proposed for elimination: [redacted] Measurement of [redacted] in process can be assessed by loss on drying. The [redacted] can be eliminated if the content uniformity testing is satisfactory.

The drug product manufacturing process has been scaled up but attempts to scale up to commercial batch size failed.

A Categorical Exclusion from the necessity to file an Environmental Assesment has been granted.

Inspection of two manufacturing sites is pending.

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

The product is intended for oral dosing four times a day for the treatment of asthma.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance is the same as in the approved NDA 20471. The drug product is adequately controlled during manufacturing up to a scale of [redacted] tablets. The tests and specifications are adequate to control the performance of the drug product except for [redacted] impurities, and total aerobic microbial count (TAMC). The acceptance criteria for these impurities should be tightened commensurate with the toxicology studies and the manufacturing process capabilities of the drug product. [redacted] The CGMP status of the facilities is acceptable except for the two foreign sites, one for the manufacture of the drug substance (form 483 issued) and the other for the manufacture of the tablet cores (inspection scheduled)

III. **Administrative** Signed off in DFS

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Blair Fraser
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INITIAL QUALITY ASSESSMENT
Office of New Drug Quality Assessment
Division of Metabolism and Endocrinology Products
NDA 22-052

Applicant: Critical Therapeutics, Inc.
Stamp Date: 31-JUL-2006 (Doc. date 30-JUL-2006)
PDUFA Date: 31-MAY-2007

Pharmacological Category: Leukotriene synthesis inhibitor
Proposed Proprietary Name: [redacted]
Established Name: zileuton controlled-release tablets (proposed)
Dosage Form and Strength: 600 mg tablets
Route of Administration: oral
Indication(s): Prophylaxis and chronic treatment of asthma in adults and children age 12 years of age and older.

PAL: Dr. Stephen Moore, Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing
Review Team Recommendation: Dr. Arthur Shaw is recommended as the primary reviewer.

Time goals:

Initial Quality Assessment in DFS: 15-SEPT-2006
Chemistry filing memo in DFS: 15-FEB-2006
Filing decision "Day 45": 29-SEP-2006 (no CMC filing issues stated at internal filing meeting 21-SEP-2006)
Filing review issues "Day 74": 13-OCT-2006
Chemistry Review (DR/IR) letter: TBD
Mid-cycle meeting "Month 5": 15-DEC-2006
Final Chemistry Review "Month 8" in DFS: 31-MAR-2006
PDUFA: 31-MAY-2006

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	Not applicable
CDRH	Not Applicable
EA	To be assessed by Primary Reviewer(s)
EES	EER sent to Office of Compliance on 17 AUG-2006. Updated 22-AUG-2006.
OSE/DMETS	Labeling consult request will be sent as part of DMEP's request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Not Applicable
Pharm/Tox	Not Applicable

SUMMARY:

Submission type: This NDA was submitted as a 505(b)(1) application with full clinical trials information. The application was submitted in paper and electronic copies, however, the CMC section is paper only. The active ingredient, zileuton, is not a new chemical entity (NCE). A conventional CMC summary is included in the application.

Clinical indication(s): [redacted] (zileuton tablets) is proposed for the prophylaxix and chronic treatment of asthma in adults and children age 12 years of age and older. Zileutin is an orally active inhibitor of 5-lipoxygenase, the enzyme that catalyses the formation of leukotrienes from arachidonic acid.

Pre-submission CMC issues and/or agreements: Investigational studies were performed under INDs 30,661 (zileutin tablets), 47,561 (zileutin CR tablets), [redacted] The following pertains to IND 47,561. A number of CMC issues and/or agreements were addressed at teleconferences held on 28-APR-2005 and 2-MAY-2005. Of these issues and/or agreements, the ones to be addressed in the NDA included: (1) provide batch results from a minimum of [redacted] lots from the [redacted], (2) provide stability data for tablet cores, provide a report on the re-evaluation of the dissolution acceptance criteria, (3) recommend to provide an [redacted] in the drug product specifications with a statement that it is controlled [redacted] stage, (4) provide all stability data (e.g., 12 months) in the initial submission and (5) provide [redacted] specifications for the drug product. The submission of stability data was addressed again at a teleconference held on 28-APR-2005. The firm's proposal to submit 6 months primary and accelerated stability data at 6 months with 9 months at the 4-month point and 9 months at the 7-month point was found acceptable.

Components and Composition of Clinical Trial Batches:

Pivotal clinical trials were conducted with formulations G and H. Formulation S6 is the same as H, except for the sites of drug substance and drug product manufacture. Bioavailability studies were conducted with formulations S6 and E21. Registration batches used formulation E21.

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Stephen Moore
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