MEMORANDUM

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

DATE: June 5, 2006

TO: the file – NDA 21-887

FROM: Pat Madara

SUBJECT: **Draft meeting minutes for End of Review meeting emailed to sponsor**

Background and Summary:

On June 6, 2005, GSK submitted a new NDA for Alli (orlistat) Capsules, 60 mg, requesting approval of Over-the-Counter status for a 60 mg strength. On April 6, 2006, an approvable letter was issued by FDA. This letter contained a list of deficiencies that required correction before approval.

On April 13, 2006, GSK submitted correspondence requesting the opportunity to discuss the content of the action letter with the appropriate Agency officials. This meeting was granted for June 14, 2006. The firm submitted a briefing package on May 17, 2006, containing specific questions for discussion. An internal pre-meeting was held on June 5, 2006.

Draft meeting minutes containing detailed answers to the questions were emailed to the company on Friday, June 9, 2006, along with a short note of explanation.

The email sent to GSK and the draft minutes are attached to this memo.

From: Madara, Patricia
Sent: Friday, June 09, 2006 4:10 PM
To: David.J.Schifkovitz@gsk.com
Cc: 'Erin.E.Oliver@gsk.com'
Subject: RE: NDA 21-887: Alternate contact info for Friday June 9

Importance: High

Attachments: end of review draft min final clean.doc

NDA 21-887

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: David J. Schifkovitz
Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Mr. Schifkovitz:

Please refer to your NDA for Alli (orlistat) Capsules, 60 mg.

We also refer to the meeting between representatives of your firm and the FDA scheduled for June 14, 2006. The purpose of the meeting is to gain Agency guidance regarding issues raised in the Approvable letter that FDA issued on April 6, 2006. In addition, reference is made to your meeting background package, submitted May 17, 2006, which included specific questions for discussion at the meeting. Draft answers to the questions are enclosed as a WORD attachment.

You have the option of canceling the meeting if these answers are clear to you. We will be prepared to clarify any questions you have regarding our responses but be advised that any new information or data not contained in your meeting package and presented in response to these draft comments will not be considered for official comment at the scheduled meeting. **Please confirm receipt of this email.**

If you have any questions, call me at (301) 796-1249.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Erin.E.Oliver@gsk.com [mailto:Erin.E.Oliver@gsk.com]
Sent: Thursday, June 08, 2006 3:35 PM
To: Madara, Patricia
Cc: David.J.Schifkovitz@gsk.com
Subject: NDA 21-887: Alternate contact info for Friday June 9

Hi Pat,

We really appreciate your efforts to issue the Agency pre-meeting minutes so quickly. As I understand it, you will try to get them out the door sometime tomorrow or Monday, June 12 at the latest.

As we discussed, I will be out of the office tomorrow (Friday, June 9). So, if you are able to finalize and distribute the minutes tomorrow, I would appreciate if you would e-mail them directly to David Schifkovitz (Director, Regulatory Affairs) with a copy to me. David's e-mail address is provided via copy of this message. Also, he can be reached at (973) 889-2509, if you have any questions or need to speak with someone.

I will return to the office on Monday, June 12. If I have not heard from you by mid-morning, I'll give you a call.

Thanks very much and have a great weekend.

Erin

Erin Oliver
Regulatory Affairs
GlaxoSmithKline Consumer Healthcare
phone (973) 889-2516

20 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 5

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(WO: 22, Mailstop 4447)

DATE RECEIVED: January 24, 2006 **DATE OF DOCUMENT:** January 20, 2006 & June 06, 2005	**DESIRED COMPLETION DATE:** March 7, 2006 **PDUFA DATE:** April 7, 2006	**ODS CONSULT #:**06-0026

TO: Mary Parks, MD
Acting Director, Division of Metabolism and Endocrinology Products, HFD-510

THROUGH: Todd Bridges, RPh., Acting Team Leader
Denise Toyer, PharmD., Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Alli**
(Orlistat Capsules)
60 mg

NDA# : **21-887**

NDA SPONSOR: **GlaxoSmithKline**

RECOMMENDATIONS:

1. DMETS does not recommend use of the proprietary name, Alli.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. Because DDMAC does not have regulatory authority to review proposed OTC proprietary names, they did not comment on the name Alli.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
WO: 22; Mailstop: 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 14, 2006

NDA#: 21-887

NAME OF DRUG: Alli
(Orlistat Capsules)
60 mg

NDA HOLDER: GlaxoSmithKline

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for assessment of the proprietary name, "Alli", regarding potential name confusion with other proprietary or established drug names. Alli is the proposed proprietary name for an over-the-counter weight loss aid containing the active ingredient, orlistat. Currently, this active ingredient is available as a prescription product in a higher strength and under a different proprietary name, Xenical. The sponsor of the prescription product is Hoffman LaRoche, Inc. Although Hoffman LaRoche will supply the drug substance to GlaxoSmithKline, we are unaware of any additional marketing arrangements. Therefore, the prescription Xenical 120 mg capsules and the OTC Alli capsules 60 mg will both be marketed at the same time. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Alli is an over-the-counter weight loss aid used to promote weight loss in overweight adults (18 years and older) when used along with a reduced calorie and low fat diet. The usual dose of Alli is one ——— capsules with each meal containing fat. The dose is not to exceed — capsules daily. ——— It will be supplied in bottles of 60, 90, and 120 capsules and in a Starter Pack containing: ——— Convenient Carrying Case, and 60 capsules.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted 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 Alli to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Alli. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Because DDMAC does not have regulatory authority to review proposed OTC proprietary names, they did not comment on the name Alli.

2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Alli. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike Names Identified by DMETS Expert Panel.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Alli	Orlistat Capsules 60 mg	One or two capsules with each meal containing fat. The maximum daily dose is six capsules.	NA
Allay	Hydrocodone Bitartrate and Acetaminophen Capsules 5 mg/500 mg	One or two capsules every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 capsules.	SA
Aleve	Naproxen Tablets 200 mg	One tablet every eight to twelve hours.	SA
Cialis	Tadalafil Tablets 5 mg, 10 mg, 20 mg	5 mg to 20 mg once daily prior to sexual activity	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

[1] MICROMEDEX Integrated Index, 2006, 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], Drugs@FDA, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

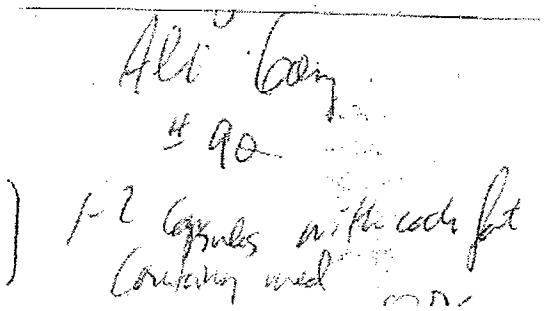
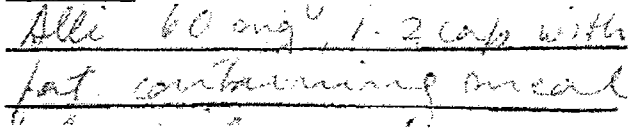
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Alli were discussed by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Alli with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 125 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Alli (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX:  	Alli 60 mg # 90 1-2 capsules with each fat containing meal.
Inpatient RX:  	

b. Allay may sound similar to Alli when spoken. Allay is indicated in the treatment of pain. Both names begin with the same three letters (All) and end in similar sounding letters (ay vs. i) which contributes to the sound-alike similarities of these two names. The phonetic similarities become more noticeable when the letter 'i' of Alli is pronounced using a short vowel sound. There are also some overlapping product characteristics that may increase confusion involving these two products. Both products are supplied in only one dosage form, one strength, have the same route of administration, and may be ordered 'as needed' or 'prn'. The 'prn' directions for use are not uncommon on an order for a pain medication, such as Allay. Additionally, since Alli is indicated to be taken at a meal containing fat, it is also possible that this product would be ordered in the same fashion so that the patient, based on the fat content of a particular meal, would decide the need for administration. However, Allay has not been marketed since 1997 and is not found in commonly used references. Therefore, despite overlapping product characteristics and the potential for similar prescribing practices, the non-availability of Allay will help to minimize confusion involving this name pair.

2. Concerns with the introduction of an OTC product prior to an RX to OTC switch

Most innovator Rx products switch to OTC prior to the introduction of competing OTC products. However, with the approval of Alli, there will be a prescription product (Xenical) and an over-the-counter product (Alli) that contain the same active ingredient (orlistat) from different manufacturers. There is a chance of confusion and potential for overdose since patients may not be aware that the two products contain the same active ingredient. The concern is the patient who augments their prescription weight loss medication and self-medicates with the over-the-counter medication in the attempt to expedite the weight loss process. This can lead to potential overdose of the active ingredient. With concurrent use of both Xenical and Alli the patient has the potential to self-administer up to 240 mg three times a day. However, the overdose information provided for the Xenical labeling states that up to 400 mg three times a day has been administered without serious adverse events. This information allays DMETS' concerns about potential overdose since this dose, 400 mg, exceeds the total dose potential for concurrent use of Alli and Xenical. Although the 240 mg dose is not a safety concern, the potential for confusion between these two drugs still exists. Therefore, the patient labeling of Alli should contain warnings that the patient check with their health care practitioner before taking Alli if they are currently taking prescription weight loss products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Alli, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (60, 90, and 120 count)

1. We note that a diacritic is located above the 'i' of the proprietary name, Alli. All information presented on the label and labeling should be presented in English. This diacritic indicates that the name originates in a language other than English. Delete this diacritic. For further guidance, we refer you to 21 CFR 201.15(c).

2. Relocate the strength so that it follows the established name and dosage form. For example see below:

Orlistat Capsules
60 mg
Weight Loss Aid

3. Revise the statement of identity so that it is presented in bold face type and presented in a font size that is reasonably related to the most prominent printed matter on the panel. In this case the proprietary name is the most prominent information on the primary display panel. Ensure that the established name is at least ½ the size of proprietary name. We refer you to 21 CFR 201.61(c) for further guidance.

4. DMETS notes that the Drug Facts are not included on any of the container labels. If these items will be sold separately from the 'Starter Pack', please revise so that the container label includes the 'Drug Facts' format as described in 21 CFR 201.66(c).

5. DMETS notes that the chemistry summary refers to a 20-count physician's sample pack. However, this was not available through the Electronic Document Room for review at this time. Additionally, physician sample packs are generally used for prescription products and not over-the-counter products. We question if this is allowable.

B. CARTON LABELING (60-count Starter Pack)

1. See comments A1 through A3.

2. 

3. DMETS notes that the label of the Starter Pack includes two different presentations of the net quantity. These two different presentations may be confusing to patients. We recommend deleting the comment '*Up to 20 days supply (60 capsules)*'.

4. The patient labeling of Alli should contain warnings that the patient check with their health care practitioner before taking Alli if they are currently taking prescription weight loss products.

Appendix A:

Outpatient Written	Verbal	Inpatient Written
Alb	Alee	Alli
Ali	Alee	Alli
Ali	Aleve	Alli
Ali	Aleve	Alli
Ali	Aleve	Alli
Ali	Aleve	Alli
Ali	Ali	Alli
Ali	Ali	Alli
Ali	Ali	Alli
Ali	Ali	Alli
Ali	Ali	Alli
Ali	Ali	Alli
Ali	Allee	Alli
Ali	Allee	Alli
Alli	Allee	Alli
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Todd Bridges
3/10/2006 09:52:33 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/10/2006 11:33:54 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/10/2006 12:44:40 PM
DRUG SAFETY OFFICE REVIEWER

27 February 2006

GlaxoSmithKline

NDA 21-887

GlaxoSmithKline
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07054-3884

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Fax. 973 889 2390
www.gsk.com

Mary Parks, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #17--CMC Update (GSK Aiken 3 Month Stability Data)

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and GSK's post-submission commitments to update the Application with —month stability data for the primary stability batches and to provide qualification data supporting Aiken, South Carolina as an alternative manufacturing site for the production of orlistat 60 mg capsules. Further reference is made to Amendment #15 submitted 06 February 2006 in which GSK provided the —month stability update for the registration batches as well as the initial qualification data supporting GSK's Aiken, SC manufacturing site (including —— stability data). Since the —— data was not available at the time of submission, GSK committed to providing this information by late February 2006. The current submission provides the —— stability update for the GSK Aiken qualification batches.

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM (~5 megabytes in size), confirmed as virus free using Symantic Antivirus Corporate Edition software (version 8.1.1.336, updated 2/26/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

23 February 2006

GlaxoSmithKline

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NDA 21-887

Mary Parks, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #16—Response to Information Request (22 February 2006)

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and to Amendment #12 submitted on 18 January 2006 containing reports of labeling studies conducted by GSK as follow-up to Actual Use Study NM17285. Further reference is made to e-mail correspondence received on 22 February 2006 from Keith Olin, Office of Nonprescription Products, requesting that GSK provide the appendices referred to in the afore-mentioned labeling studies. A copy of this correspondence is provided herein for reference.

The current amendment provides the requested information. For completeness, this submission contains the complete study reports, including all appendices, for the Warfarin Self-Selection Study and Teen Self-Selection Study and is intended to replace those previously submitted in Amendment #12. No changes have been made to the content of the study reports beyond addition of the appendices and associated bookmarks/hyperlinks.

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM (~ 10 megabytes in size), confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.1.1.336, updated 2/22/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

MEMORANDUM

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

PID #: 050738

DATE: February 8, 2006

FROM: Cynthia Kornegay, Ph.D., Epidemiologist
Division of Drug Risk Evaluation
Office of Drug Safety

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation
Office of Drug Safety

TO: Mary Parks, M.D., Acting Director
Division of Metabolic and Endocrine Drug Products
Office of New Drugs

SUBJECT: Review of potential association between orlistat and pancreatitis

IND/NDA #: 020766

Executive Summary

The purpose of this consult is to assess the sponsor's analysis of the potential association between orlistat and pancreatitis. This review complements the January 23, 2006 Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee meeting addressing a proposal to make orlistat available without a prescription.

This review of the sponsor's data mining analysis using disproportional reporting rates of pancreatitis associated with orlistat determined that although preliminary, it failed to recognize the effect that a small and selective database can have on the magnitude and significance of reporting rate findings. When the analysis was done in FDA's Adverse Event Reporting System, a larger and more general data resource, a small but statistically significant signal was observed.

A data mining analysis should never be the sole indicator of the presence or absence of a safety signal, since a positive finding does not necessarily translate to a true safety signal, while the absence of a finding is not an assurance that no signal exists. Data mining is a measure of association, but cannot assess causality. However, when supported by a detailed case analysis and additional clinical and epidemiologic data, it may provide further evidence for a safety signal.

Introduction

Orlistat (Xenical®) was approved in April 1999 for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. Orlistat is indicated for patients with an initial BMI $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 in the presence of other risk factors (e.g. hypertension, diabetes, dyslipidemia).

Prior drug safety consults have investigated associations between orlistat and thyroid dysfunction[1], diabetes[2], cardiovascular outcomes[3,4], fatal outcomes[5-7], and a drug interaction with cyclosporine[8]. The current consult is an assessment of an analysis the sponsor performed to examine the association between orlistat and pancreatitis.

Due to the nature of the analysis, the Division of Metabolic and Endocrine Drug Products requested that ODS review the sponsor's results.

Methods

On November 23, 2004 the sponsor submitted a report that analyzed 86 case reports of pancreatitis associated with orlistat use. The sponsor's conclusions were based on analysis using the proportional reporting ratio (PRR). This consult will describe the sponsor's methods and analysis, comment on the sponsor's findings, and will also briefly describe a preliminary PRR analysis conducted using the Adverse Event Reporting System (AERS) database.

Proportional Reporting Ratio/Rate

The proportional reporting rate or ratio (PRR) is a disproportionality measure that is suited to large databases. It was first used in drug safety the early 1990's, although was already being used in other fields, and a similar measure, the proportional mortality ratio, was a well-known epidemiologic measure[9]. The statistic compares the proportion of the occurrence of a particular event to the total number of events for a particular drug to the same proportion for the rest of the database. It is calculated as follows:

	Event of Interest	All Other Events
Drug of Interest	a	b
All Other Drugs	c	d

$$PRR = \frac{a/(a+b)}{b/(b+d)}$$

The null value of the PRR is 1. If the PRR is greater than 1, then the event of interest occurs more often with the drug of interest than with other drugs in the database. The statistical significance of the PRR is determined by a chi-square with 1 degree of freedom. If the chi-square value is greater than 4, then the PRR is statistically significant.[10, 11]

The PRR has several advantages: it is easy to calculate and interpret, does not require additional denominator information, and counteracts some of the biases related to variable reporting. As the number of reports increases, the PRR is as good a disproportionality measure as other, more complicated, techniques, such as Bayesian data mining. Because the PRR summarizes and compares large quantities of data, it is amenable to use in very large databases, such as AERS, and may catch drug safety signals that might otherwise be missed.[10-12]

It does have some notable limitations, however. The PRR is a measure of relative reporting, which may not reflect the relative occurrence of the event in the general population. High levels of reporting for a particular drug may reduce the magnitude of associations for other potential signals with the same drug due to denominator inflation. Similarly, a very strong signal for a drug class may reduce the magnitude of signals for that same event in other drugs due to numerator inflation. If the database is small or contains clusters of drug classes, the comparator group bias could hide potential signals. The PRR, like other data mining statistics, is a measure of association, not causation. Finally, it is also important to remember that the PRR has the same limitations as any other analysis of spontaneous adverse event data. In particular, a significant PRR does not automatically indicate a valid safety signal, nor does a non-significant PRR mean that the signal should not be examined in detail.[10-13]

For these reasons, the PRR is most often used in practice as a hypothesis-generating tool rather than a confirmatory analysis. Organizations use the PRR in combination with other clinical and epidemiologic

assessment strategies as well as post-marketing case adjudication to determine which potential signals need to be investigated further and to determine causality.[11, 12, 14]

Results

The sponsor included all case reports (clinical trial and spontaneous, serious and non-serious) of pancreatitis that were in their database as of November 30, 2002. The preferred terms used for the search were: amylase increased, pancreatic disorder NOS, pancreatic enzymes NOS increased, pancreatitis, and enzyme abnormality. The following system organ classes were included: Gastro-intestinal System Disorders, Metabolic and Nutritional Disorders. A total of 86 reports were retrieved. Of these, 10 were excluded due to lack of medical confirmation (i.e., direct consumer reports) and 2 were in blinded clinical trials, leaving a total of 74 reports available.

The PRR analysis used 72 event reports, with a cutoff date of September 1, 2002. Although not specified in the report, this could have included multiple events for a single case. To compensate for possible bias due to orlistat's known association with certain gastrointestinal events, the WHOART preferred terms of abdominal pain, diarrhea, flatulence, rectal disorder, and steatorrhea were excluded from the PRR calculation. PRR results were provided both with and without the excluded terms:

Event Preferred Term	No. of Reports	PRR w/ Exclusions	Significance (p-value)	Overall PRR (no exclusions)
Pancreatic Disorder NOS	3	1.73	$p>0.05$	1.09
Pancreatitis	57	0.73	$p\leq 0.05$	0.46
Amylase Increased	6	0.47	$p>0.05$	0.30
Enzyme Abnormality	6	0.65	$p>0.05$	0.41

Based on these results the sponsor concluded that no signal for an association between orlistat and pancreatitis was present in their database.

At FDA's request, an updated PRR analysis was done with a cutoff date of December 31, 2004. In the updated analysis, there were 84 events for acute and chronic pancreatitis (higher level term) and 9 events for blood amylase increased (preferred term) or pancreatic enzyme increased (preferred term). The PRR results for both analyses were 1.17 (compared to 1.09 in the original analysis). Neither PRR was statistically significant, so the sponsor again concluded that these results did not indicate that a safety signal might be present.

Unrelated to the PRR analysis, the sponsor also searched the General Practice Research Database (GPRD) for pancreatitis cases among patients treated with orlistat between the years 1999 – 2002. There were 7066 patients who received orlistat during that period. Among this cohort of patients, 11 patients were diagnosed with pancreatitis during that time frame. In 5 patients the diagnosis was prior to a record of an orlistat prescription, five had a diagnosis after a prescription for orlistat, and in one the date of the pancreatitis diagnosis is unknown. Based on this analysis, the sponsor concluded that the chance of experiencing pancreatitis was approximately the same both before and after a prescription for orlistat.

Discussion

While a PRR analysis is a valuable tool, it must be used and interpreted with care. It should not be used as the sole indicator of a potential safety signal – a careful review of clinical evidence is always necessary.[9-22] In addition, the PRR denominator, all the other drugs in the database, can have a profound influence on the magnitude of a particular signal.[22] While it can help to isolate a signal if events are selectively removed such as consumer reports, this removal must be done throughout the database. In the sponsor's analysis, the entire database should have been restricted to non-consumer reports, but it appears that this restriction was applied to orlistat-related events only. Failure to restrict all events in the same manner could be a source of bias, and could serve to obscure a potential signal.

Another concern is the use of an appropriate comparison group. Smaller and more selective comparison groups can mask potentially significant signals.[22] Heeley (2002)[11] provides the specific example of hallucinations with tolterodine to illustrate the importance of choosing the appropriate comparator group. When the crude PRR was calculated for this association in the U.K.'s Presciption Event Monitoring database, there was not a significant signal. This could have been due to the fact that this is a small, selective database of solicited events, and several of the comparator drugs were antipsychotics and antidepressants, which have a known association with hallucinations. When the antipsychotics and antidepressants were removed from the calculation, the PRR increased in magnitude and became highly statistically significant. This is an analogous situation to PRR calculations using sponsor databases. These data resources are likely to be smaller and more selective than AERS, and to have selected drugs or drug groups represented rather than a cross-section of all drugs. Since this data mining technique performs best with large amounts of non-selective data, the AERS database is an ideal resource to do these types of calculations.

To examine the possibility of comparator bias, a preliminary PRR analysis was performed in AERS for orlistat. Unlike the sponsor analysis, the AERS investigation did not exclude any terms, and was adjusted by age, gender, and FDA receipt date. As expected, the gastro-intestinal events commonly associated with orlistat showed as very strong, significant signals. Acute pancreatitis (17 cases), pancreatitis (73 cases), and blood amylase increased (14 cases) had less strong associations, but were also statistically significant. If, as could be the case, the signals for gastro-intestinal disorders are biasing the PRR, then the actual safety signal might be stronger than these initial results indicate. This is not a confirmation of a safety signal, but should be interpreted as a potential signal that would require more investigation, including a detailed case analysis.

The preliminary GPRD investigation performed by the sponsor could not be duplicated. When a medical practice is added to the GPRD database, historical or retrospective information as well as prospective data is added. Thus, even if the analysis were restricted to the same time period as the sponsor, there is likely to be more and different information available. Another possible concern with the use of GPRD is the lack of available hospital information. Since GPRD does not collect data on hospitalizations, there could be a considerable delay before the GP records a pancreatitis episode, and the relevant hospital tests may not be available. However, given the seriousness of this condition, some indication of the diagnosis would likely be in the patient's record. Should an investigation be done in this data resource, the sponsor would need to provide objective evidence that pancreatitis is reliably, consistently, and accurately captured by GPRD.

In summary, the sponsor's PRR investigation, although preliminary, fails to take into account the effect that a small and selective database can have on the magnitude and significance of the PRR. When a parallel, preliminary analysis was done in AERS, indications were that a safety signal may be present. Although the PRR should never be the sole indicator of the presence or absence of a safety signal, if supported by additional clinical information, it does provide further evidence for a safety signal in this particular case.

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/s/

Cynthia Kornegay
2/13/2006 02:21:04 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
2/13/2006 04:48:06 PM
MEDICAL OFFICER

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08 February 2006

NDA 21-887

Mary Parks, M.D., Deputy Director
Food and Drug Administration
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Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #14--Response to FDA Questions (received 18-20 January 2006)

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and the information request received by GlaxoSmithKline (GSK) on 18 January 2006 as well as the follow-up request received on 20 January 2006 from Keith Olin, Office of Nonprescription Products (via e-mail). Both requests pertained to GSK's Actual Use Trial (study NM17285).

GSK responded to the first request on 19 January 2006 and the follow-up request on 08 February 2006, via email. This amendment constitutes GSK's formal submission of this information to NDA 21-887. Enclosed please find the original information request and GSK's formal response. Please note that no changes have been made to the content of the response as submitted previously via e-mail (provided herein as references).

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM (~ 5 megabytes in size), confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.1.1.336, updated 2/7/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

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06 February 2006

NDA 21-887

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5901-B Ammendale Road
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Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #15--CMC Update

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and GSK's commitments to provide updated CMC information during the review cycle (Ref: No21887\Reviewer's Guide\Post-Submission Commitments). Specifically, GSK committed to updating the Application with [redacted]-month stability data for the [redacted] primary stability batches and providing qualification data to support Aiken, South Carolina as an alternative manufacturing site for the production of orlistat 60mg capsules. These commitments were agreed in the December 8, 2004 Pre-NDA Meeting and discussed in a CMC teleconference held on March 23, 2005.

This Amendment provides the [redacted]-month stability update for the registration batches. Additionally, this submission provides the initial qualification data supporting GSK's Aiken, SC manufacturing site. These qualification data include the initial bulk, in-process and finished product data, multipoint dissolution profile comparisons and [redacted]-month stability data for [redacted] full-scale batches qualification batches. The [redacted] month stability data will be provided in a separate Amendment, targeted for submission by late February 2006.

For reviewer reference, the Pre-Approval Inspection of GSK's Aiken facility was recently completed (17 January -26 January 2006; Inspector Bonita Chester). As per Inspector Chester, GSK Aiken currently has a satisfactory GMP inspection status for the type of operation that is being considered (CHG; capsule prompt release).

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM (~ 15 megabytes in size), confirmed as virus free using Symantic Antivirus Corporate Edition software (version 8.1.1.336, updated 2/5/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

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31 January 2006

NDA 21-887

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Division of Metabolism and Endocrinology Products
Food and Drug Administration
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #13 -- Tradename Labeling

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and GSK's commitment to update the Application with the brand name selections for the product and behavioral support program in a December 2005-January 2006 timeframe (Ref: No21887\Reviewer's Guide\Post-Submission Commitments). Further reference is made to Amendment #6 submitted to the Agency on 21 November 2005 in response to a request by the Office of Nonprescription Products to provide a sample starter pack. Within that response, GSK communicated our decision regarding the product tradename and provided a prototype OTC package for orlistat 60 mg capsules, labeled to reflect the tradename "Alli" (pronounced al-eye).

In a follow-up conversation with Patricia Madara (Regulatory Project Manager, Division of Metabolism and Endocrinology Products), GSK was requested to submit copies of all proposed labeling, updated to reflect the selected tradename, to facilitate review and approval by the Office of Drug Safety. To expedite the review process, GSK sent a representative set of updated labels to the Agency via e-mail on 20 January 2006 (e-mail to Patricia Madara). These labels are identical to those that appear in the current submission.

The current submission formally responds to the Agency's request and fulfills GSK's tradename commitment by providing revised labeling (bottle, carton, and in-pack materials) whose content has been modified solely to reflect the selected brandnames for the product (Alli) and the behavioral support program (MyAlliPlan).

The amendment is provided in electronic format. This electronic portion of the submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM of approximately 15 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.00.9374, updated 1/31/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

MEMORANDUM

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

DATE: January 19, 2006

TO: NDA 21-887

FROM: Laura Shay, PM

SUBJECT: **Informal meeting requested by GSK to discuss** the upcoming AC meeting for Orlistat 60 mg

On January 10, 2006, David Shifkovitz and John Dent from GSK met with Andrea Leonard-Segal, Acting Division Director of the Division of Nonprescription Clinical Evaluation (DNCE) and Laura Shay, Project Manager for DNCE to inquire if they could discuss their plan for post-marketing studies on adolescents and enhanced warnings on the label at the January 23, 2006 Advisory Committee meeting. GSK was told that this information would be fine to present at the AC meeting as long as they stated that this information has not been submitted to the FDA for review.

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

/s/

Laura Shay
1/19/2006 06:51:53 PM
CSO

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17 January 2006

NDA 21-887

Mary Parks, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #12--Submission of Additional Labeling Studies to Support Proposed OTC Label

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and to the Advisory Committee Briefing Document submitted on 19 December 2005 in which GlaxoSmithKline (GSK) described three labeling studies that had been conducted post-NDA submission as a follow-up to the sponsor's Actual Use Trial (study NM17285).. Specifically, GSK conducted targeted self-selection studies in the following populations of interest: cyclosporine users, warfarin users and teens.

The content of these three studies was summarized in GSK's briefing document (refer to Section 8.4 Post-NDA Targeted Consumer Research) and discussed briefly with the Agency in a meeting that took place on 10 January 2006 between representatives of the Office of Nonprescription Products and GSK.

The purpose of the current amendment is to provide the final study reports for these three labeling studies for the Agency's consideration and review. These studies are contained in Item 8F Other Studies and Information (N021887\clinstat).

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM (~ 10 megabytes in size), confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.1.1.336, updated 1/16/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

David Ashworth for Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

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NDA 21-887

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Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #11--Response to FDA Questions (received 04 January 2006)

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and the request for clarification regarding the level of dietary instruction provided in study NM17247 received by GlaxoSmithKline (GSK) on 04 January 2006 from Patricia Madara, Division of Metabolism and Endocrinology Products.

GSK responded to this request on 11 January 2006 via email. This amendment constitutes GSK's formal submission of this information to NDA 21-887. Enclosed please find the original information request and GSK's formal response. Please note that no changes have been made to the content of the response as submitted previously via e-mail (provided herein as reference).

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM (~ 5 megabytes in size), confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.1.1.336, updated 1/16/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Gerard Ackerman for Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

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17 January 2006

NDA 21-887

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5901-B Ammendale Road
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Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #10--Response to FDA Questions (received 13 & 19 Dec 2005)

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and the information request received by GlaxoSmithKline (GSK) on 13 December 2005 from Keith Olin, Office of Nonprescription Products. The content of this information request related to GSK's final Label Comprehension Study (N021887\clinstat\84fb). Further reference is made to a follow-up information request received on 19 December 2005 from Patricia Madara, Division of Metabolism and Endocrinology Products, on behalf of Keith Olin (ONP).

GSK responded to this request on 22 December 2005 via email. For reference, a copy of this e-mail correspondence is provided in the current submission (without attachments).

This amendment constitutes GSK's formal submission of this information to NDA 21-887. Enclosed please find the original information request and GSK's response to each item noted therein. Please note that no changes have been made to the content of the response as submitted previously via e-mail.

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM of approximately 5 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.1.1.336, updated 1/16/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

David Ackerman for Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

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16 January 2006

NDA 21-887

Mary Parks, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #9--Response to FDA Clinical Questions (received 29 Nov 2005)

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and the clinical information request received by GlaxoSmithKline (GSK) on 29 November 2005 from the Division of Metabolism and Endocrinology Products (via e-mail).

In order to expedite Agency review, GSK responded to this request via email and provided answers as they become available. The complete response was forwarded directly to Patricia Madara, Regulatory Project Manager, Division of Metabolism and Endocrinology Products via two separate e-mails. Parts 1 and 2 of GSK's response were sent on 05 December 2005 and 07 December 2005, respectively. For reference, a copy of this e-mail correspondence is provided in the current submission (without attachments).

This amendment constitutes GSK's formal submission of this information to NDA 21-887. Enclosed please find the original information request and GSK's response to each item noted therein. Please note that no changes have been made to the content of the response as submitted previously via e-mail.

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM of approximately 10 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.1.1.336, updated 1/12/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

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13 January 2006

NDA 21-887

Mary Parks, M.D., Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #8--Response to FDA Clinical Questions

Dear Dr. Parks,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and the clinical information request received by GlaxoSmithKline (GSK) on 28 November 2005 from the Office of Nonprescription Products (via e-mail).

In order to expedite Agency review, GSK responded to this request via email and provided answers as they become available. The complete response was forwarded directly to Keith Olin, Regulatory Project Manager, Office of Nonprescription Products via three separate e-mails. Parts 1, 2 and 3 of GSK's response were sent on 30 November 2005, 02 December 2005 and 05 December 2005, respectively. For reference, a copy of this e-mail correspondence is provided in the current submission (without attachments).

This amendment constitutes GSK's formal submission of this information to NDA 21-887. Enclosed please find the original information request and GSK's response to each item noted therein. Please note that no changes have been made to the content of the response as submitted previously via e-mail.

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM of approximately 10 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.1.1.336, updated 1/12/2006).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

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19 December 2005

NDA 21-887

Advisors and Consultants Staff
FDA, CDER, OEP, ACS
HFD-21, Room 1093
5630 Fishers Lane
Rockville MD 20852-1734
Attention: Darrell Lyons

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Briefing Document for 23 January 2006 Advisory Committee Meeting

Dear Mr. Lyons,

Reference is made to our pending New Drug Application (NDA) 21-887 submitted 06 June 2005 for the use of Orlistat 60 mg Capsules as an over-the-counter weight loss aid in conjunction with a reduced calorie and low fat diet. Further reference is made to your correspondence of 04 November 2005 in which you confirmed that GlaxoSmithKline's (GSK) NDA would be the subject of an upcoming Advisory Committee meeting and requested the submission of a background information package.

The purpose of this correspondence is to provide the briefing document for the 23 January 2006 joint meeting of the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committee.

In accordance with the draft guidance, *Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of new Drugs and Convened by the Center of Drug Evaluation and Research, Beginning on January 1, 2000*, we are providing the briefing document 22 business days prior to the scheduled advisory committee meeting. It is a fully releasable background document and all copies have been marked **"AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION"**. The briefing document contains no confidential or trade secret information and may be posted without redaction on the FDA internet site 24 hours prior to the meeting.

As requested, please find enclosed 40 paper copies and 2 electronic copies of the briefing document. The electronic submission is included on one CDROM of approximately 5 megabytes in size. The CDROM has been confirmed as virus free

using Symantic Antivirus Corporate Addition software (Program 8.1.1.336, updated 12/18/2005).

It is our understanding that you will provide GSK with a copy of the CDER background package in advance of the advisory committee meeting. As per the aforementioned guidance, we anticipate receiving this information by COB 14 days prior to the scheduled advisory committee meeting. Please let me know if you foresee any changes to the timing of receipt of FDA materials.

Thank you in advance for your assistance in this matter. If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

Cc: NDA 21-877

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21 November 2005

NDA 21-887

David Orloff, M.D., Director
Division of Metabolism and Endocrinology Products
Food and Drug Administration
Office of Drug Evaluation II
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5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #6 -- Response to FDA Request (Sample Starter Pack)
Communication of Proposed Trade Name

Dear Dr. Orloff,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and the information request received by GlaxoSmithKline (GSK) on 12 October 2005 from Keith Olin, Project Manager in the Office of Nonprescription Products related to the proposed package and label for OTC orlistat 60 mg capsules.

Description of Agency Request

Specifically, the Agency requested the following information (request enclosed):

- enlarged paper copies of proposed OTC labeling for the refill carton (90 and 120 cts) and the starter pack (drug facts panel)
- a mock up of the Orlistat starter kit -- to gain understanding of how the educational material would be presented to the consumer.

GSK Response

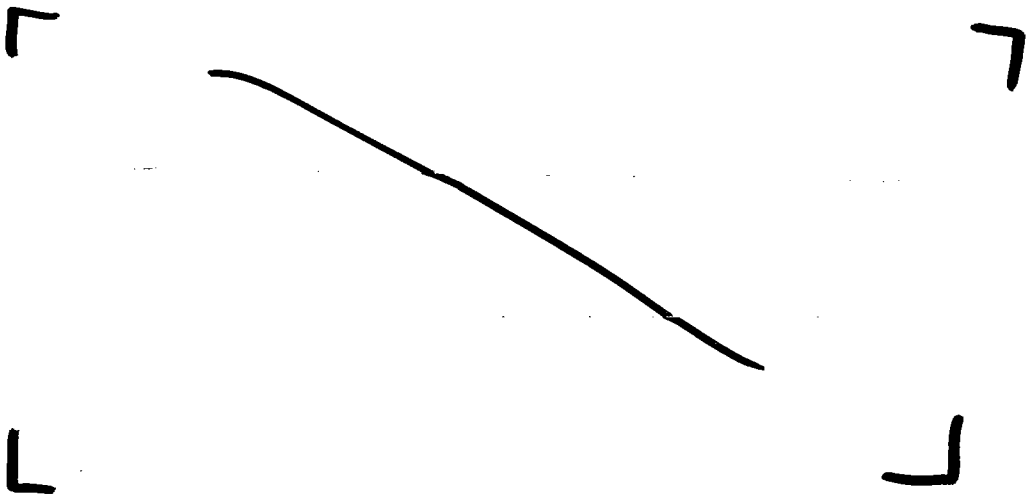
GSK responded to the first of the two requests on 18 October 2005 (General Correspondence: Response to Labeling Request). In the same correspondence, GSK noted that additional time was required to respond to the second request as a prototype of the proposed OTC starter pack was not immediately available and would require custom fabrication. We therefore indicated our intent to respond to the second request separately in a future correspondence.

Fabrication of the prototype is now complete. The current submission provides a sample of the intended consumer starter pack, complete with in-package educational materials and proposed OTC labeling.

Description of Orlistat 60 mg Starter Package

The orlistat OTC Starter Pack is a multipiece package containing a single bottle of orlistat 60 mg capsules; a complete set of dietary reference guides and tools (Welcome Card, Companion Guide, Healthy Eating Guide, Calorie and Fat Counter, QuickFacts Card, and Daily Journal); and a temporary carrying case.

The prototype included in the current submission is intended to simulate a commercial package and thus, reflects aspects of the proposed labeling as described in the NDA. The Sponsor notes, however, that the current prototype does not reflect all aspects and design features of the final commercial package. For example,



In terms of label content, the only difference from the labels as they appeared in the original NDA (No21887\Item 2 Labeling) is the replacement of the placeholder [BRANDNAME] text with the proposed tradename for orlistat 60 mg capsules.

Proposed Tradename

Recall that at the time of NDA submission, the process of trademark registration had not yet been finalized and GSK used the term [BRANDNAME] as placeholder text throughout the draft labeling. Further, GSK had committed to updating the Application with the final product brand name selection in a December 2005-January 2006 timeframe (Ref: No21887\Reviewer's Guide\Post-Submission Commitments).

GSK is taking this opportunity to communicate our decision in this matter and requests FDA consideration and approval of "Alli" (pronounced al-eye) as the trade name for orlistat OTC 60 mg capsules. [1]

Number of Units Provided

[redacted]

Material is Proprietary -- Confidentially is Requested

We consider the information contained in this submission to be CONFIDENTIAL and not to be disclosed to any person outside of the Food and Drug Administration without prior notification and written consent of GlaxoSmithKline.

The amendment is provided in both paper and electronic format. This electronic portion of the submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM of approximately 1 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.00.9374, updated 11/20/2005).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

---

[1] Final selection of the Behavioral Support brand name is pending; this information will be available for submission as originally intended by January 2006.

GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

11 November 2005

NDA 21-887

David Orloff, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #5--Response to FDA Clinical Questions

Dear Dr. Orloff,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and the clinical information request received by GlaxoSmithKline (GSK) on 27 October 2005. Enclosed please find the original information request and GSK's response to each item noted therein.

This submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM of approximately 15 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.00.9374, updated 11/9/2005).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

MEMORANDUM

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

DATE: October 31, 2005

TO: the file

FROM: Pat Madara

SUBJECT: **Comments and information request for the applicant**
NDA 21-887 (orlistat) tablets (OTC)

Background and Summary:

This NDA has been submitted in support of 60 mg orlistat capsules (for over-the-counter use) as an aid to weight loss.

In order to complete review of the clinical section of the application, the medical officer, Dr. Julie Golden, required some additional information.

These requests were conveyed to the applicant via voice mail and email (to Erin Oliver, Regulatory Affairs).

The sponsor was instructed to submit all responses officially to the IND and reference this request.

My email and the WORD attachment to GlaxoSmithKline are attached to this memo.

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, October 27, 2005 1:18 PM
To: 'Erin.E.Oliver@gsk.com'
Subject: NDA 21-887 clinical info request

Dear Erin:

Please refer to your NDA 21-887 for orlistat, 60 mg.

Also, please refer to the WORD document attached to this email. We are reviewing the Clinical section of your NDA and request the information detailed in the attached document.

clinical info
equest.doc (32 .

Please confirm receipt of this email. You may reply to this request via email but also submit your responses officially to your NDA and cite this request.

ALL regulatory submissions, whether sent by U.S. Postal Service, overnight mail service, or courier, should be sent to the following address. Processing of submissions sent to other addresses may be delayed.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1249.

Sincerely,

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Queries:

1. Do the mean weight loss analyses over time and the categorical analyses in the pooled studies include site 12327 from study NM14161? If not, please provide updated analyses including this site.

2. In the ISE, statistical testing on BMI and anthropometry change was not provided. Were these changes statistically significant from placebo?

3. Study BM14150 was not included in the ISE, although Table 1 under 8B indicates this study has an efficacy role in the OTC NDA. Please either explain why it should not be included in the ISE, or summarize results from this study as applicable to the efficacy of the 60 mg dose to complement the findings from the other studies in the ISE.

4. Please provide a categorical analysis of subjects in the pooled studies who lost $\geq 5\%$ of baseline body weight at 4 months.

5. Please provide an efficacy analysis (either least mean squares difference from placebo or categorical) and an AE table from study NM17247 without Dr. [redacted] site included.

6. Please provide, from pooled data from studies 149 and 161, the mean and median absolute and % placebo-subtracted changes in bodyweight from baseline to Month 6 for the orlistat 60 mg and 120 mg groups for the following 3 BMI cohorts:

   - < 30 kg/m^2; 30-35 kg/m^2; and > 35.1 kg/m^2

   Please provide results for the ITT (LOCF) and Completers populations separately.

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

/s/

Patricia Madara
10/31/2005 12:26:30 PM
CSO

GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

18 October 2005

NDA 21-887

David Orloff, M.D., Director
Division of Metabolism and Endocrinology Products
Food and Drug Administration
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
General Correspondence--Response to FDA Request (Labeling)

Dear Dr. Orloff,

Enclosed please find GlaxoSmithKline's response to a request for labeling information identified in a phone conversation between myself and Keith Olin, Regulatory Project Manager, Office of Nonprescription Products on 12 October 2005.

This correspondence includes the original request and GSK's response. Specifically, this response provides enlarged images of certain proposed OTC labels for Orlistat 60mg Capsules in both electronic and paper format. Please note that the electronic labeling contained in the current submission is unchanged from that provided in Amendment #3, submitted on 16 August 2005.

In the same conversation, FDA requested a sample of the actual starter package, including complete copies of in-package materials. GSK is currently investigating the availability of materials and timing required to respond to this request. Therefore, GSK intends to address this request separately in a future correspondence.

The electronic portion of this submission complies with the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999) and is included on one CDROM of approximately 10 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.00.9374, updated 10/17/2005).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolism and Endocrinology Products
Keith Olin, Office of Nonprescription Products

GlaxoSmithKline

06 October 2005

NDA 21-887

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3804

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Fax. 973 889 2390
www.gsk.com

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #4 -- Safety Update Report (120-day)
Corrections to Clinical Data Tables and Financial Disclosure Information

Dear Dr. Orloff,

Pursuant to CFR §314.50 (d)(5)(vi)(b), GlaxoSmithKline (GSK) herewith updates the above referenced pending application with new safety data for the reporting period of 01 December 2004 through 15 August 2005. As no clinical investigations associated with NDA 21-887 are ongoing, this amendment provides an update to general safety information related to orlistat as it appeared in Item 8H (Integrated Summary of Safety) and Item 9 (Safety Update) of the original application.

Further, in response to the Agency's interest in foreign marketing experience of orlistat in any OTC markets, this amendment summarizes safety data available for Australia and New Zealand, two foreign markets in which Xenical® has been reclassified as an OTC (behind-the-counter) medicine.

All data are consistent with the original NDA and this Safety Update has not revealed any new safety issues or areas or concern.

Additionally, this amendment provides corrections to clinical information as described below:

- During a review of the final report for study [redacted] an error was discovered in 3 study tables contained in the original application. GSK is providing corrected, replacement tables in this submission.

- On 26 September 2005, GSK received a phone call from the Agency indicating that during the course of review of NDA 21-887, the Medical Officer discovered that financial disclosure information was missing for 2 investigators from study [redacted] This information was inadvertently omitted from the original application and is provided herein.

This submission complies with the guidance for industry titled **Providing Regulatory Submissions in Electronic Format – NDAs (January 1999)** and is included on one CDROM of approximately 20 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.00.9374, updated 9/29/2005).

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

for Erin Oliver

Erin Oliver
Manager, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC: Patricia Madara, Division of Metabolic and Endocrine Drug Products
Keith Olin, Office of Nonprescription Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-887
IND 62,758

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Erin Oliver
Manager, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Oliver:

Please refer to your submission dated June 6, 2005, requesting a waiver for pediatric studies for orlistat, 60mg.

We have reviewed the submission and agree that a waiver is justified only for pediatric studies in patients ages 0 to 11 years for orlistat, 60 mg, for promotion of weight loss, because use by this age group may be ineffective and/or unsafe in an over-the-counter (OTC) setting.

Pediatric studies in patients ages 12 to 17 years for orlistat, 60 mg, for promotion of weight loss, are being deferred under 505B(a)(4) of the Federal Food, Drug and Cosmetic Act (the Act) until October 7, 2009 in order to obtain additional post-marketing experience of the OTC product.

The requirements for your deferred pediatric study or studies will be fully addressed upon approval of this product. Deferred studies will be considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81.

If you have questions, please call Pat Madara, Regulatory Project Manager, at 301-827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Mary Parks
8/18/2005 09:30:21 AM
for Dr. Orloff

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

FILING COMMUNICATION

NDA 21-887

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Erin Oliver
Manager, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Oliver:

Please refer to your June 6, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for orlistat tablets, 60 mg.

We also refer to your submissions on June 10, and August 2, 2005.

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 August 6, 2005 in accordance with 21 CFR 314.101(a).

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

- Your correspondence dated August 2, 2005, received August 3, 2005, states that submission of Registration Batch and Qualification data for the Aiken, South Carolina facility may be delayed beyond the December 2005 – January 2006 timeframe. If such a delay occurs, the user fee goal date may be extended by three months to provide time for a full review of the submission.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Patricia Madara
8/16/2005 03:21:27 PM
Pat Madara signing for Kati Johnson

GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
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07054-3884

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www.gsk.com

16 August 2005

NDA 21-887

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #3 -- Response to FDA Information Request

Dear Dr. Orloff,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005 and the Agency's request for information received via e-mail on 10 August 2005 (from Patricia Madara, Division of Metabolic and Endocrine Drug Products) in which the Agency requested (1) enlarged copies of proposed OTC labeling and (2) minor revision of certain Label Comprehension Study summary tables (Ref. Item 8.F.4.b) to present data in terms of both number (n) as well as percentage (%).

This correspondence is intended to fully respond to the above request. The submission complies with the guidance for industry titled **Providing Regulatory Submissions in Electronic Format – NDAs (January 1999)** and is included on one CDROM of approximately 10 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.00.9374, updated 8/15/2005.

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Manager, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC (cover letter):
Patricia Madara, Division of Metabolic and Endocrine Drug Products (DMEDP)
Keith Olin, Office of Nonprescription Products (ONP)

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, August 10, 2005 10:25 AM
To: 'Erin.E.Oliver@gsk.com'
Cc: Olin, Keith
Subject: NDA 21-887 Information requests

Dear Erin:

Please refer to your June 6, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for over-the-counter (OTC) orlistat tablets .

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. You may reply via email but also submit any responses officially to the NDA and cite this request.

- Resubmit files for the following labels, enlarging the print to allow for easier viewing:
  refill90.pdf
  refill120.pdf
  strpall.pdf
  strttp60.pdf
  strttp90.pdf
  strtp120.pdf

- Provide results in tables that report the "n" as well as percentages. The following table is an example of the preferred organization but it is presented for illustrative purposes only.

Base: Total Responding	General Population N = 304		Low Literacy N = 160	
	N	%	N	%
Correct (total)	?	?	?	?
Correct initially Q90				
Not okay	?	?	?	?
Ask her doctor	?	?	?	?
Correct after probe Q91				
Ask a doctor first	?	?	?	?
Ask a doctor/pharmacist	?	?	?	?
Acceptable (total)	?	?	?	?
Acceptable initially Q90				
Call the 800#	?	?	?	?
Acceptable after probe Q91				
Look in User Guide	?	?	?	?
Incorrect (total)	?	?	?	?
Is not contraindicated	?	?	?	?
Okay to use	?	?	?	?

Package does not mention	?	?	?	?
Lower dosage	?	?	?	?
Don't know	?	?	?	?

If you have any questions, call me at (301) 827-6416.

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Patricia Madara
8/16/2005 04:12:01 PM
CSO

MEMORANDUM OF TELECON

DATE: August 9, 2005

APPLICATION NUMBER: NDA 21-887 orlistat, 60 mg capsules

BETWEEN:

Name: Erin Oliver
Phone: 973-889-2516
Representing: GlaxoSmithKline

AND

Name: Pat Madara, Regulatory Project Manager
Division of Metabolism and Endocrinology Products, HFD-510

SUBJECT: Information request

Background and Summary:

NDA 21-887 is currently under review for the 60 mg strength of orlistat capsule OTC (over-the-counter use). The proposed indication is promotion of weight loss. The application is being reviewed jointly by DMEDP and DOTCDE.

Keith Olin, project manager in DOTCDE forwarded a request from DOTCDE reviewers for some additional information from the company. I contacted Erin Oliver on August 9, 2005 and asked if this request could be sent via email. She indicated that was acceptable.

Therefore, this information request was relayed via telephone call (requests explained on 8/9/05) and email sent on August 10, 2005. Receipt of email was confirmed by Ms. Oliver. My email is attached to this document.

Note; the firm was instructed to submit responses officially to the NDA and cite this request.

Pat Madara
Regulatory Project Manager

GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

02 August 2005

NDA 21-887

David Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-887 (Orlistat 60 mg Capsules)
Amendment #2 (CMC) -- Update to Manufacturing Site Change Proposal

Dear Dr. Orloff,

The following correspondence relates to the proposal to qualify GlaxoSmithKline's Aiken, South Carolina facility as a manufacturing site for the production of bulk orlistat 60 mg capsules. Reference is made to the qualification proposal outlined in original NDA 21-887 (CMC Section 4.A.2.e-1 Drug Product Manufacturers) submitted 06 June 2005.

The estimated timings for site completion and data availability were initially discussed with the Agency in a teleconference held on 23 March 2005 between representatives of GlaxoSmithKline Consumer Healthcare (GSK) and members of the Division of New Drug Chemistry and Division of Metabolic and Endocrine Drug Products. In a follow-up communication to the Agency (submitted 29 March 2005) GSK provided an updated and expanded summary of key events and timings which estimated completion of manufacturing qualification activities in mid-September, 2005. This target timeframe for inspection readiness of the Aiken facility was also reflected in NDA 21-887 Form 356h.

Separately, GSK communicated the planned activities and timeline to the Atlanta District to ensure the Field Office was informed of potential future workload. This direct communication was particularly important in light of the pending general cGMP inspection of the Aiken facility in 2005. The potential to consolidate

inspectional activities and conserve resources was considered to be mutually beneficial and in the best interests of both GSK & Agency.

Recognizing that GSK Aiken site readiness is associated with the completion of multiple, complex activities (i.e. facility construction, equipment delivery/installation, batch manufacture/testing), the purpose of this correspondence is to communicate the progress made to date and update the Application with the current timeline for completion of key Aiken site qualification activities.

GSK welcomes the opportunity to closely collaborate with the Agency to efficiently manage these pending inspectional requirements. GSK has been requested to direct all communications related to the PAI for NDA 21-887 through the Division of Metabolic and Endocrine Drug Products (conversation with P. Madara, 21 July 2005). Given the continued desire to coordinate inspectional activities and the high priority the Atlanta District has placed in completing the Aiken general cGMP audit, GSK respectfully asks that the present correspondence be shared with the appropriate District personnel.[1]

Independent of discussions related to NDA 21-887 PAI, GSK will continue its dialogue with the Atlanta District in scheduling of the imminent general cGMP inspection of the Aiken facility.

The submission complies with the guidance for industry titled **Providing Regulatory Submissions in Electronic Format – NDAs (January 1999)** and is included on one CDROM of approximately 3 megabytes in size. The CDROM has been confirmed as virus free using Symantic Antivirus Corporate Addition software (version 8.00.9374, updated 7/21/2005.

[1] GSK notes that the scheduling of inspections is left to the discretion of the District within time frames assigned by the reviewing Division and that Districts may contact manufacturers directly to determine the readiness of facilities for inspection since "facilities or the development of manufacturing processes may not have been completed or changes in the status of the application may have occurred" (per FDA Compliance Program Guidance Manual , program 7346.832 (Pre-Approval Inspections/Investigations), implemented April 5, 2005).

To ensure the Field Copy remains an exact copy of the Chemistry section of NDA 21-887, this updated CMC information is also being communicated to the Field Office under separate cover.

If you have any questions concerning this submission, please contact me by phone at (973) 889-2516 or by FAX at (973) 889-2501.

Sincerely,

Erin Oliver

Erin Oliver
Manager, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

CC (cover letter):
Patricia Madara, Division of Metabolic and Endocrine Drug Products (DMEDP)
Keith Olin, Office of Nonprescription Products (ONP)

MEMO TO FILE

FROM:	WEI QIU, Ph.D.
TO:	NDA 21-887
SUBMISSION DATE:	June 6, 2005
SUBJECT:	Filing of the original submission of orlistat 60 mg capsules

The sponsor GSK submitted an original NDA for orlistat 60 mg capsules as an Over-The-Counter (OTC) weight loss aid on June 6, 2005. The sponsor incorporate cross-references to the Hoffmann-La Roche NDA 20-766 for Xenical® as agreed in the pre-NDA meeting held on December 8, 2004 and there is no new information on clinical pharmacology and biopharm.

Since the detectable plasma concentrations of orlistat at therapeutic dose are low and infrequent, and the OTC switch dose is the half of the approved prescription dose, review of the clinical pharmacology is not necessary.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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/s/

Wei Qiu
7/19/05 09:55:18 AM
BIOPHARMACEUTICS

Hae-Young Ahn
7/22/05 05:27:30 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-887

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Erin Oliver
Manager, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Oliver:

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

Name of Drug Product:	orlistat tablets, 60 mg
Review Priority Classification:	Standard (S)
Date of Application:	June 6, 2005
Date of Receipt:	June 7, 2005
Our Reference Number:	NDA 21-887

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 6, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 7, 2006.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Division Document Room, Rm 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Patricia Madara
7/11/05 12:51:03 PM

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

June 10, 2005

NDA 21-887

Charles Ganley, M.D.
Director
Office of Nonprescription Drugs
Division of Nonprescription Clinical Development
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, HFD-560
9201 Corporate Boulevard
Rockville, MD 20850

Re: Amendment #1 to NDA 21-887 - Orlistat 60 mg Capsules

Dear Dr. Ganley,

Reference is made to original NDA 21-887 submitted to the Agency on 06 June 2005.

During a routine post-submission quality check of the electronic submission for NDA 21-887, it was noticed that some PDF bookmarks were incorrectly pointing to files on a GSK Consumer Healthcare network server instead of pointing to files within the electronic submission structure.

Specifically, we have determined that 6 documents contained bookmarks that required repair to correct the link to the destination document. The table below lists all repaired documents included in this amendment intended to replace those in the original submission.

Document Name	Location	Reason for Replacement
Ndatoc.pdf	N021887	All bookmarks and links incorrectly pointed to GSK network share drive
Cover.pdf	N021887	Original file supplied without bookmarks
356h.pdf	N021887	Original file supplied without bookmarks
Product.pdf	N021887\cmc\product	3 bookmarks incorrectly pointed to GSK network share drive
Clintoc.pdf	N021887\clinstats	All bookmarks and TOC links incorrectly pointed to GSK network share drive
Othertoc.pdf	N021887\other	All bookmarks and TOC links incorrectly pointed to GSK network share drive

The CD-ROM included in this amendment contains the replacement documents listed above. They have been organized in their respective eNDA folders to aid in the replacement process.

GlaxoSmithKline certifies that no changes have been made to the content of the submission and that this file replacement is solely intended to address technical issues and improve navigation capability.

This electronic submission is included on 1 CD-ROM which has been confirmed as virus free using Symantec Antivirus software (version 8.00.9374, scan engine 4.1.0.15, 5/25/2005 Rev 18).

Please contact my office at (973) 889-2516 with any questions regarding this submission. In my absence, please contact David Schifkovitz at (973) 889-2509. If you have a particular question about technical aspects of electronic format, please contact Gregory Smith (Regulatory Operations, GlaxoSmithKline Consumer Healthcare at (973) 889-2540).

Sincerely,

Erin Oliver

Erin Oliver
Manager, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare

June 6, 2005

NDA 21-887

GlaxoSmithKline
257 Cornelison Avenue
Jersey City, NJ
07302-3198

Tel. 201 434 3000
www.gsk.com

Charles Ganley, M.D.
Director
Office of Nonprescription Drugs
Division of Nonprescription Clinical Development
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, HFD-560
9201 Corporate Boulevard
Rockville, MD 20850

Re: New Drug Application - Original
Orlistat 60 mg Capsules

Dear Dr. Ganley,

In accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, GlaxoSmithKline (GSK) hereby submits an original New Drug Application (NDA) for orlistat 60 mg capsules as an Over-The-Counter (OTC) weight loss aid. The application submission and review incorporates cross-references to the Hoffmann-La Roche NDA 20-766 for Xenical® as described in the enclosed Reviewer's Guide and as agreed in our December 8, 2004 Pre-NDA meeting.

The NDA is provided in electronic format only and is consistent with the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - NDAs (January 1999)". The electronic submission is included on 4 CDROMs. Each CDROM has been confirmed as virus free using Symantec Antivirus software (version 8.00.9374, scan engine 4.1.0.15, 5/25/2005 Rev 18).

Please contact my office at (973)889-2516 with any questions regarding this submission. In my absence, please contact David Schifkovitz at (973) 889-2509. If you have a particular question about technical aspects of electronic format, please contact Gregory Smith (Regulatory Operations, GlaxoSmithKline Consumer Healthcare at (973)889-2540).

Sincerely,

Erin Oliver

Erin Oliver
Manager, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: August 31, 2005.
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
GlaxoSmithKline Consumer Healthcare, L.P.	June 6, 2005
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(973) 889-2516	(973) 889-2501
APPLICANT ADDRESS *(Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, Zip Code, telephone & FAX number) IF APPLICABLE*
1500 Littleton Road Parsippany, NJ 07054-3884	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): NDA 21-887

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
orlistat	TBD

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(If any)*
Tetrahydrolipstatin	Ro-18-0647

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule (banded hard gelatin)	60 mg	oral

(PROPOSED) INDICATION(S) FOR USE:

Promote weight loss in overweight adults when used along with a reduced calorie and low fat diet

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Original Application for OTC Weight Loss Indication

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION DRUG PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full Establishment information should be provided in the body of the Application)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-766* (Xenical), IND 31,617*, IND 62,758 *see enclosed Authorization from Hoffmann-La Roche

	This application contains the following items: *(Check all that apply)*
X	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d)(1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e)(2)(i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d)(2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d)(3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d)(4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d)(5), 21 CFR 601.2)
X	9. Safety update report (e.g. 21 CFR 314.50 (d)(5)(vi)(b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d)(6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f)(1), 21 CFR 601.2)
X	12. Case report forms (e.g. 21 CFR 314.50 (f)(2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k)(3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Erin Oliver	**Erin Oliver** **Manager, Regulatory Affairs**	06 June 2005

ADDRESS *(Street, City, State, Zip Code)*	Telephone Number
1500 Littleton Road, Parsippany, NJ, 07054-3884	**(973) 889-2516**

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (4/03)

Attachments for FDA Form 356h - orlistat 60 mg capsules

Chemical Name:
Tetrahydrolipstatin
(S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester

Establishment Information:

Drug Substance Manufacturer (orlistat)
Name:
Address:

Contact:
Telephone No.:
Registration No.:
DMF No.:
Manufacture Steps/Type of testing performed at site:
Ready for Inspection:

Drug Product Manufacturer:
Name:
Address:

Contact:
Telephone No.:
Registration No.:
DMF No.:
Manufacture Steps/Type of testing performed at site:
Ready for Inspection:

Drug Product Manufacturer:

Name:	Glaxo Wellcome Division SmithKline Beecham Corp
Address:	1011 North Arendell Avenue Zebulon, North Carolina 27597

Contact:	[redacted]
	Site Quality Director
Telephone No.:	919-269-1045
Registration No.:	1033964
DMF No.:	N/A
Manufacture Steps/Type of testing performed at site:	Gelatin capsule banding (sealing) site
Ready for Inspection:	Yes

Drug Product Manufacturer:

Name:	GlaxoSmithKline Consumer Healthcare
Address:	Verenes Industrial Park 65 Windham Blvd. Aiken, South Carolina 29805
Contact:	[redacted]
Telephone No.:	803-642-6105
Registration No.:	1046838/ATL
DMF No.:	N/A
Manufacture Steps/Type of testing performed at site:	Drug product manufacture, gelatin capsule banding, testing and bulk/finished product packaging and labcling
Ready for Inspection:	Mid-September, 2005

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,758

GlaxoSmithKline
Attention: Erin Oliver
Manager, US Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Oliver:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for orlistat OTC 60 mg capsules.

We also refer to your amendment dated February 1, 2005 (serial # 022), containing a request to amend the January 7, 2005, meeting minutes reflecting the Pre-NDA meeting between FDA and GSK on December 8, 2004.

We have completed the review of your submission and have the following comments and recommendations.

Comments from the Division of Metabolic and Endocrine Drug Products (DMEDP):

1. **GSK requests that the meeting minutes reflect their discussion of the efficacy of the 60 mg oristat dose.**

   The FDA appraisal reflected in the minutes is that any assessment of efficacy should follow the current guidelines for weight loss agents. Although disagreement may exist as to whether the 60mg dose is efficacious, this is ultimately a review issue and would not be decided until all available data has been reviewed with the NDA submission. We acknowledge that GSK discussed that the 60 mg dose is an effective dose, however, that does not suggest that we agree with the interpretation of the results.

Comments from the Office of Nonprescription Drug Products:

2. **GSK requests that the meeting minutes contain the following statement regarding the selection of the optimal dose for OTC use:**

   We agree to add GSK's statement to the January 7, 2005, meeting minutes as it stands on page 3 of their February 1, 2005, submission:

   "Therefore, the Sponsor herein restates its intention to pursue a dose of 60 mg to 120 mg for OTC use of orlistat as a weight loss aid. We believe this agreement addresses the Agency's

concern with respect to optimal therapeutic dose selection and that no further action on the part of the Sponsor is required."

3. **GSK requests that FDA clarify the Rx indication for orlistat verses the OTC indication, the BMI range for OTC orlistat, and the labeling to reflect weight loss in an overweight OTC population.**

   - The Proposed Rule for Weight Control Products for Over-the-Counter Human Use, published February 26, 1982, recognizes weight control and weight loss as OTC indications.
   - The following indications should remain prescription indications: longer-term treatment exceeding six months for obesity management and treatment of co-morbidities.
   - In the NDA submission, the sponsor will need to justify restricting the labeled OTC population to individuals age 18 and older.
   - The Drug Facts label should reflect use of the product as a weight loss aid.
   - The OTC population can include a wide range of BMIs ranging from slightly overweight to obese.
   - The "overweight" population is acceptable for OTC.

4. **GSK requests clarification on whether or not an additional actual use study will be needed.**

   - If the already completed actual use study plus the results from studies NM14161 and NM17247 can distinguish between the weight loss caused by orlistat alone and the weight loss caused by the behavioral interventions alone, then another actual use study may not be needed. If another actual use study is needed, we recommend discussing the protocol design with the Agency.

If you have any questions, call Keith Olin, Regulatory Project Manager, at 301-827-2293.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over the Counter Drug Products
Center for Drug Evaluation and Research

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

/s/

Charles Ganley
5/3/05 02:34:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,758

GlaxoSmithKline Consumer Healthcare
Attention: Erin Oliver, Manager, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Oliver:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenical (Orlistat) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2004. The purpose of the meeting was to review the progress of the Orlistat Rx to OTC switch and confirm the content and format of the proposed submission.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6381.

Sincerely,

{See appended electronic signature page}

Oluchi Elekwachi, PharmD, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Wednesday, December 8, 2004
TIME: 12PM-1:30 PM
LOCATION: Parklawn Potomac Conference Room
APPLICATION: 62,758
DRUG NAME: OTC Orlistat (GlaxoSmithKline)
TYPE OF MEETING: Type B – Pre NDA

MEETING CO-CHAIRS: David G. Orloff, MD and Charles Ganley, MD

MEETING RECORDER: Oluchi Elekwachi, PharmD, MPH

FDA ATTENDEES:

Name	Title
ODE II	
Robert J Meyer, MD	Director
HFD-510 DMEDP	
Kati Johnson	CPMS
David G Orloff, MD	Director
Eric C Colman, MD	Medical Team Leader
Julie Golden, MD	Medial Officer
Lee Ping Pian, PhD	Statistician
Wei Qiu, PhD	Biopharmaceutics Reviewer
Oluchi Elekwachi, PharmD, MPH	Project Manager
Theresa Kehoe, MD	Medical Officer
HFD-560 DOTCP	
Andrea Leonard Segal, MD	Medical Team Leader
Charles J Ganley, MD	Director
Karen Feibus, MD	Medical Officer
Neel Patel, PharmD	IDS
HFD-400 ODS	
Lanh Green, PharmD, MPH	Team Leader
Mary Dempsey	Project Manager
HFD-820 DNDC II	
Eric P Duffy, PhD	Director
Martin T Haber, PhD	Chemistry Reviewer
Sheldon B Markofsky, PhD	Chemistry Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Mr. David Schifkovitz Director, Regulatory Affairs, Project Leader for orlistat Rx to OTC Switch Mr. George Quesnelle President, Consumer Healthcare North America
Dr. John Dent Senior Vice President, Research and Development
Mr. Steve Burton Vice President, Weight Control Business Unit
Dr. Jonathan Hauptman Clinical Science Leader, Xenical ® , Hoffmann- La Roche, Inc.
Dr. Randy Koslo Director, Medical Affairs

Dr. Vidhu Bansal Principal Clinical Scientist, Medical Affairs
Dr. Cecilia Hale Senior Statistician, Biostatistics and Data Management
Ms. Erin Oliver Manager, Regulatory Affairs
Dr. Susan Schwartz Director, New Product Research
Dr. Satish Dipali Group Leader, New Product Development

BACKGROUND:

IND 62,758 was submitted by Hoffman-La Roche, Inc. on July 14, 2001 supporting the Rx to OTC switch of orlistat. There was an End of Phase II meeting held on July 17, 2002 between representative of Roche and the Division of Metabolic and Endocrine Drug Products and Division of Over the Counter Drug Products. GlaxoSmithKline (GSK) has acquired ownership of this IND from Roche, Inc. GSK plans to submit its NDA for OTC Orlistat in May of 2005.

In addition to the studies previously reviewed in the initial Orlistat marketing application, three studies were done under the 60mg IND 62,758:

RCH-ORL-002: a 4-week, open-label, non-randomized, uncontrolled study of 60mg Orlistat use in a naturalistic setting. Population: BMI 27-57, mean BMI 35.

NM17247: a 16-week, randomized, double-blind, placebo-controlled trial to evaluate the safety and effectiveness of Orlistat 60mg plus diet in patients with BMI 25-28. Population: BMI 24-29, mean BMI 27. Diet: hypocaloric.

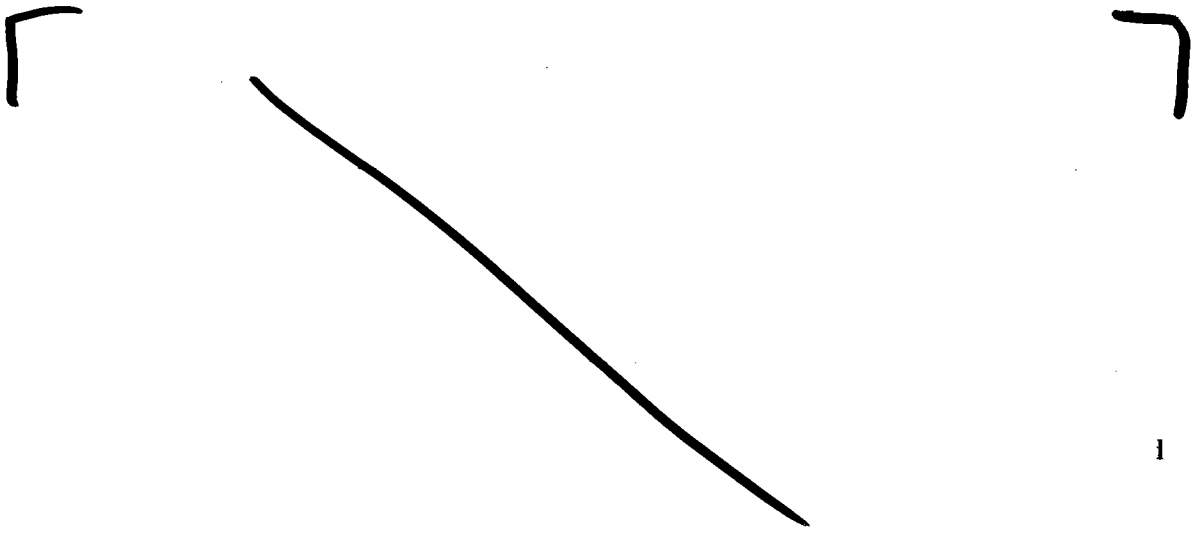
NM17285: a pilot, multi-center, pharmacy-based, open-label, all comers, 3 month study conducted under actual use conditions. Population: BMI 21-54, mean BMI 32.

The briefing package was submitted on November 2, 2004

MEETING OBJECTIVES:

GSK intends to outline how the previously identified issues will be addressed in the application and obtain comments on format and content of the proposed NDA submission for orlistat OTC.

DISCUSSION POINTS:



1

9 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

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Withheld Track Number: Administrative 6

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

/s/

Oluchi Elekwachi
1/7/05 05:52:31 PM

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 21-887 Supplement # Efficacy Supplement Type SE-

Trade Name: TBD
Established Name: orlistat
Strengths: 60 mg

Applicant: GlaxoSmithKline
Agent for Applicant:

Date of Application: June 6, 2005
Date of Receipt: June 7, 2005
Date clock started after UN:
Date of Filing Meeting: July 18, 2005
Filing Date: August 6, 2005
Action Goal Date (optional): User Fee Goal Date: April 7, 2006

Indication(s) requested: Promote weight loss in overweight adults; weight loss aid

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
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 is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification (1,2,3 etc.): 5
Other (orphan, OTC, etc.): OTC

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

User Fee Status: Paid ☒ 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. 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 an approved (b)(1) or (b)(2) application? YES ☒ NO ☐

If yes, explain: Hoffman-LaRoche holds exclusivity for the 120 mg strength product (Xenecal, Rx). They have sold rights to the 60 mg strength to GlaxoSmithKline who are seeking approval for OTC marketing as a weight loss aid.

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

- 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 ☒

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 ☐

If no, explain:

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

- Is the submission complete as required under 21 CFR 314.50? YES ☒ NO ☐

If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
If an electronic NDA, all forms and certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format? all

Additional comments: I do not have the original paper administrative/regulatory forms since this application was originally managed by OTC and they still have the jackets.

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Was the patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Was exclusivity requested? YES, _____ 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 ☒ 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 ☐

- 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 ☒ NO ☐

- Were financial disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 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)? Y ☒ NO ☐

- Are the PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Are the trade, established, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
  Is the established name correct in COMIS IND(s) file(s): YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- List referenced IND numbers: 62,758; 31,617

- End-of-Phase 2 Meeting(s)? Date(s) July 17, 2002 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) December 8, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ 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 ☐ NO ☒
  If no, did applicant submit a complete environmental assessment? YES ☒ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 18, 2005

NDA #: 21-887

DRUG NAMES: orlistat capsules, 60 mg

APPLICANT: GlaxoSmithKline

BACKGROUND: Hoffman LaRoche holds NDA 20-766 for Xenical (orlistat) Capsules, 120 mg; a prescription drug indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL Rx is also indicated to reduce the risk for weight regain after prior weight loss. NDA 21-887 is now submitted for the 60 mg strength of orlistat capsule as an OTC (over-the-counter) drug. The proposed indication is promotion of weight loss; weight loss aid. The application is being reviewed jointly by DMEDP and DOTCDE. The OTC NDA is held by GlaxoSmithKline who purchased the rights to this size orlistat capsule.

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

ATTENDEES: In addition to the assigned reviewers listed below, the following were attendees at the filing meeting:
Dr. Robert Meyer, Office Director, ODE II
Dr. David G. Orloff, Director, DMEDP
Dr. Eric Colman, Clinical Team Leader, DMEDP
Dr. Jeri D. El Hage, P/T Team leader, DMEDP
Dr. Hae Young Ahn, Clinical Pharmacology Team Leader for DMEDP
Dr. Todd Sahlroot, Biometrics Team Leader for DMEDP
Dr. Charley Ganley, Office Director OND/ONP/DOTCDE
Dr. Curtis Rosebraugh, Acting Director; DOTCDE
Dr. Andrea Leonard-Segal, Clinical Team Leader for DOTCDE
Dr. Arlene Solbeck, IDS/DOTCDE
Dr. Mamta Gautam Basak, Chemistry Team Leader for DMEDP
Dr. Helen Cothran, Team Leader for IDS/DOTCDE

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

Discipline	Reviewer
Medical:	Julie Golden, DMEDP;
Secondary Medical:	Karen Feibus, DOTCDE
Statistical:	Joy Mele, DMEDP; Stan Lin, DOTCDE
Pharmacology:	Fred Alavi, DMEDP
Statistical Pharmacology:	NN
Chemistry:	Martin Haber for DMEDP
Environmental Assessment (if needed):	not needed - exclusion granted

Biopharmaceutical:	Wei Qiu, DMEDP, no review needed
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	NN
Regulatory Project Management:	Pat Madara, DMEDP; Keith Olin, DOTCDE
Other Consults:	Susanna Weiss, DOTCDE

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known January 23, 2006 NO ☐
- 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 ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☐

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☒
- Microbiology 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:

☐ 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.

☒ Filing issues to be communicated by Day 74. List (optional): delay in facility inspection or submission of registration batch and qualification data will delay goal date.

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.

Pat Madara
Regulatory Project Manager, HFD-510

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) 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.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES ☐ NO ☐

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference? YES ☐ NO ☐
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES ☐ NO ☐
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? N/A ☐ YES ☐ NO ☐
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted? YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application? YES ☐ NO ☐

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

/s/

Patricia Madara
8/24/2005 03:02:34 PM
CSO

NDA: 21-887

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X		
2) Is the clinical section of the NDA adequately indexed and paginated in a manner to allow substantive review to begin?	X		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	X		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e. appropriately designed dose-ranging studies)?	X		
5) On its face, do there appear to be the requisite number of adequate and well-controlled studies submitted in the application?	X		See attached.
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X		
7) Are all data sets for pivotal efficacy studies complete for all indications requested?	X		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X		
9) Has the applicant submitted line listings in a format to allow reasonable review of patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			NA (pivotal studies were performed in US)
11) Has the applicant submitted all additional required case report forms (beyond deaths and, drop-outs) previously requested by the Division)?			NA. CRFs for deaths and drop-outs included.

ITEM	YES	NO	COMMENT
12) Has the applicant presented the safety data in a manner consistent with center guideline and/or in a manner previously agreed to by the Division?	X		
13) Has the applicant presented a safety assessment based on <u>all</u> current world-wide knowledge regarding this product?	X		Published literature is included.
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	X		OTC labeling: 201.66.
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	X		
16) From a clinical perspective, is this NDA fileable? If not, please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

Reviewing Medical Officer / Date

Supervisory Medical Officer

Study No. / Study Completion Date	Type of Study	Role in OTC NDA	Duration	BMI	Dose	Individual Datasets Included?	Data Included in Pooled Datasets?	CRFs Included?
BM14149 February 1996 N20-766	Weight loss study	Safety & Efficacy	2 yrs	28-43	Placebo 60 mg 120 mg	No	Yes	No***
NM14161 February 1995 N20-766	Weight loss study using primary care providers	Safety & Efficacy	2 yrs	30-43	Placebo 60 mg 120 mg	No	Yes	No***
NM17247 October 2003 N21-877	Weight loss study in a primary care setting	Safety & Efficacy	4 mos	25-28	Placebo 60 mg	Yes	Yes	Yes
BM14150 May 1995 N20-766	Dose-ranging study	Safety & Efficacy	6 mos	28-43	Placebo 30 mg 60 mg 120 mg 240 mg	No	No	No***
NM14302 March 1996 N20-766	Weight maintenance effect of orlistat after 6 month period of weight loss by diet alone	Safety	18 mos*	28-38	Placebo 30 mg 60 mg 120 mg	No	Yes (Safety only)	No***
RCH-ORL-002 December 2001 N21-877	Evaluation of orlistat in a naturalistic setting	Supportive	4 wks	**	60 mg	Yes	No	Yes
NM17285 October 2003 N21-877	Pilot actual use study	Supportive	3 mos	**	60 mg	Yes	No	Yes

*12 months of drug treatment

** These studies were intended to simulate an OTC environment; no BMI restrictions were imposed

*** Cross-referenced to NDA 20-766

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

/s/

Julie Golden
7/20/05 11:20:29 AM
MEDICAL OFFICER

Eric Colman
7/20/05 11:34:05 AM
MEDICAL OFFICER

7 Page(s) Withheld

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