CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-887

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-887

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline Consumer Healthcare, L.P.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
TBD

ACTIVE INGREDIENT(S)	STRENGTH(S)
Orlistat, tetrahydrolipstatin	60 mg

DOSAGE FORM
Capsule, Oral

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 4,598,089	7/1/1986	6/18/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
HLR Technology Corporation	Mr. George W. Johnston 340 Kingsland Street	
	City/State Nutley, NJ	
	ZIP Code 07110-1199	FAX Number *(if available)* 973 235 2363
	Telephone Number 973 235 3656	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Theodore R. Furman	April 4, 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Theodore R. Furman	
Address GlaxoSmithKline 709 Swedeland Rd. Corporate IP - US (UW 2220)	City/State King of Prussia, PA
ZIP Code 19406	Telephone Number 610 270 6857
FAX Number *(if available)* 610 270 5090	E-Mail Address *(if available)* Theodore.R.Furman@GSK.com

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

PSC Media Arts (301) 443-1090 EF

EXCLUSIVITY SUMMARY

NDA # 21-887 SUPPL # HFD #

Trade Name Alli capsules

Generic Name 60 mg orlistat

Applicant Name GlaxoSmithKline

Approval Date, If Known 7-Feb-2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years under 314.108 (b)(4)(iv)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20766 Xenical (120 mg orlistat) capsules

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

NM17247 - Weight loss study in primary care setting - 4 month
NM17285 - Actual use study - 3 month

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

NM17247 - Weight loss study in primary care setting - 4 month
NM17285 - Actual use study - 3 month

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 62758 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # 62758 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐ ! NO ☐

Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Keith Olin
Title: Project Manager
Date: 3/7/07

Name of Office/Division Director signing form: Andrea Leonard-Segal, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Andrea Segal
3/9/2007 07:53:42 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-887 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: June 7, 2005 **Action Date:** April 6, 2006

HFD 510 **Trade and generic names/dosage form:** Alli (orlistat) Capsules
Applicant: GlaxoSmithKline **Therapeutic Class:** 3021850

Indication(s) previously approved: indicated for obesity management including weight loss and weight maintenance when used in conjunction with a redced-calorie diet. Also indicated to reduce the risk for wight regain after prior weight loss. Indicated for obese patients with an initial body mass index (BMI) $\geq$ 30kg/m^2 or $\geq$ 27 kg/m^2 in the presence of other risk factors.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Weight loss aid, to promote weight loss in overweight adults when used with a reduced calorie, low fat diet (action on 4/6/06 was approvable)
Is there a full waiver for this indication (check one)?

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.** 0	**yr.** 0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.** 0	**yr.** 11	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **XX There are safety concerns** Use by this age group may be ineffective and/or unsafe in an OTC setting
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

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
4/6/2006 04:33:02 PM

Item 16

Debarment Certification

NDA 21-887

Orlistat 60mg Capsules

Consumer Healthcare
1500 Littleton Road
Parsippany, NJ 07054-3884

Debarment Certification

Pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Janice McSherry, Assistant General Counsel

4/4/05
Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-887	Efficacy Supplement Type SE-	Supplement Number	
Drug: Alli (orlistat) Capsules, 60 mg		Applicant: GlaxoSmithKline	
RPM: Keith Olin		HFD-560	Phone # 301-796-0962

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Type 8
• Other (e.g., orphan, OTC)	OTC (N)
❖ User Fee Goal Dates	April 7, 2006, 2nd cycle Feb 7, 2007
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "Yes," skip to question (4) below. If "No," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE - April 7, 2006
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	Feb 1, 2007
• Original applicant-proposed labeling	**Carton, drug facts, and brochure label**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	03/10/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	Labeling, 1/9/07, 1/11/07,1/31/07,2/5/07
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	none
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	1/31/07; 1/30/07; 6/9/06; 10/16/06; 1/19/06
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	July 17, 2002
• Pre-NDA meeting (indicate date)	December 8, 2004
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other Regulatory Briefing	March 21, 2006
❖ Advisory Committee Meeting	
• Date of Meeting	January 23, 2006
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	DMEP/clin TL (EC) 3/21/06; DNCE TL (BN) 12/26/06 DMEP/DD (MHP) 3/22/06 ODE 2 (CR) 4/4/06; 2/6/07 DNCE DD (AS) 3/21/06; 1/16/07 ONP (CG) 4/6/06; 2/7/07
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	DMEP 3/8/06 OTC actual use 3/6/06; OTC label comp 3/14/06, 11/27/06; 12/21/06
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NN
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	12/20/06
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	2/7/07
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	3/8/06
❖ Biopharmaceutical review(s) *(indicate date for each review)*	NN
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NN
❖ Clinical Inspection Review Summary (DSI)	NN
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	February 23, 2006
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	February 23, 2006
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NN
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	NN
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
GlaxoSmithKline Consumer Healthcare, L.P.
1500 Littleton Road
Parsippany, NJ 07054-3884

2. TELEPHONE NUMBER *(Include Area Code)*
(973) 889-2516

3. PRODUCT NAME
Orlistat 60 mg Capsules

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021887

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4914

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, 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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
David Schlichenmeyer	Director, Regulatory Affairs	April 5, 2005

FORM FDA 3397 (1/03)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
See attached list	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David Schifkovitz	Director, Regulatory Affairs
FIRM/ORGANIZATION GlaxoSmithKline Consumer Healthcare 1500 Littleton Road Parsippany, NJ 07054	
SIGNATURE David Schifkovitz	DATE 4-4-05

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

TO BE COMPLETED BY APPLICANT

The following information concerning C _____)
Name of clinical Investigator
who participated as a clinical investigator in the submitted study C _____
_____)
Name of clinical study
is submitted in accordance with 21 CFR part 54.

The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkbox.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME David Schifkovitz	TITLE Director, Regulatory Affairs
FIRM/ORGANIZATION GlaxoSmithKline Consumer Healthcare	
SIGNATURE David Schifkovitz	DATE 4-05-05

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information, Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room I4C-03
Rockville, MD 20857

OTC Drug Labeling Review

Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#:	**21-887**
Submission Date:	February 1, 2007
Type of Submission:	Original New Drug Application/BL
Sponsor:	GlaxoSmithKline
Drug Product:	Orlistat OTC
Active Ingredient:	•Orlistat, 60 mg in each capsule
Indication:	•promotes weight loss in overweight adults when used along with a reduced calorie and low fat diet
Stock Keeping Units:	4 (60 capsule starter pack, 90 capsule starter pack, 120 capsule starter pack, 120 capsule refill pack)
Review Date:	February 2, 2007
Reviewer:	Arlene Solbeck Division of Nonprescription Regulation Development
Project Manager:	Keith Olin Division of Nonprescription Clinical Evaluation

Background

Orlistat is a pancreatic lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. Hoffmann-La Roche, Inc. first submitted an investigational new drug application (IND 31,617) for orlistat capsules in May, 1988.

On April 23, 1999, FDA approved NDA 20-766 for the prescription-only marketing of Xenical®, orlistat 120 mg tid. FDA approved a pediatric indication for ages 12-16 on June 12, 2004.

On June 19, 2001, FDA received a Hoffman-La Roche, Inc. application for IND 62,758 to investigate the development of orlistat for OTC marketing. In September 2004, GSK acquired ownership of IND 62,758 from Hoffman-La Roche, Inc. GSK has right of reference to relevant information within IND 31,617 and NDA 20-766, but the ownership of and responsibility for these two applications remain with Roche.

OTC Orlistat Timeline:

- On June 6, 2005 GSK submitted NDA application 21-887 for OTC marketing of 60 mg orlistat capsules tid.
- On January 24, 2006 the Nonprescription Drugs and the Endocrine and Metabolic Drugs Advisory Committees met to discuss the safety and efficacy of OTC use of orlistat.
- FDA issued an approvable letter (AE) on April 6, 2006 to GSK.
- On April 13, 2006 GSK submitted an official request for an end-of-review meeting with FDA. A briefing document, containing a specific list of questions for discussion, was received on May 17, 2006.
- FDA sent answers to the questions to GSK on June 9, 2006.
- GSK and FDA met on June 14, 2006 to discuss specific issues related to the design of GSK's proposed label comprehension and self-selection study protocols, and also revised labeling for OTC marketing of orlistat.
- On August 4, 2006, GSK resubmitted NDA 21-877 in response to FDA's approvable letter.
- On December 22, 2006, some labeling comments were faxed to GSK.
- On January 9, 2007, GSK and FDA participated in a labeling discussion via T-con, in response to FDA's December 22, 2006 fax. More labeling comments were emailed to GSK on January 12, 2007.
- GSK's revised labeling, which constituted a complete response to FDA's December 22, 2006 labeling review, and revisions requested by FDA in January 2007, was received on January 17, 2007.
- FDA requested revised labeling from GSK on January 25, 2007.
- GSK responded to FDA on January 30, 2007 with a question about one of FDA's recommendations in the January 25th request. FDA responded with an answer on 1/31/07.
- This current submission provides revised labeling and constitutes GSK's complete response to FDA's requested labeling revisions of January 25 and January 31, 2007. GSK requested that FDA should refer to GSK's submission of January 17, 2007 for the text and graphic specifications used in the Drug Facts portion of the Starter Pack and Refill carton.

This current submission contains the following for review:

- Starter Pack Labels (60, 90, 120ct) consisting of PDP (Principal Display Panel),Top label, and Back Label (Drug Facts) presented separately
- Refill Carton, 120ct
- Bottle Labels (60, 90, 120ct)
- Read Me First (Keys to successful weight loss)

Reviewer's Comments

In FDA's correspondence to GSK dated January 25, 2007 and January 31, 2007, FDA requested the following labeling revisions:

A. Starter Pack and Refill Carton Labeling/PDP and Top Panels

1. On the top panel of the Starter Pack, under "*The Starter Pack includes*:", delete reference to the Welcome Guide, Companion Guide, QuickFacts Cards, Healthy Eating Guide, Calorie & Fat Counter, and Daily Journal. It is acceptable to add, in their place, a phrase such as "For more information, visit www.MyAlli.com", which is similar to a statement under the **Drug Facts** box which reads "For more information and to learn more about Alli, visit us at **www.MyAlli.com**."

FDA's Response: GSK deleted reference to the Welcome Guide, Companion Guide, QuickFacts Cards, Healthy Eating Guide, Calorie & Fat Counter, and Daily Journal. GSK added the phrase, "For more information, visit ***www.MyAlli.com***. These changes are acceptable. The Starter Pack labels for the 60ct, 90ct and 120ct packages are acceptable with one exception: the parts of the label that are printed in light grey should be made darker to enhance readability. This can be done at the next printing.

2. On the carton labeling of the Refill Pack under "The Refill Pack includes", delete reference to the Companion Guide and substitute reference to the Read Me First brochure instead.

FDA's Response: GSK deleted reference to the Companion Guide and added reference to the Read Me First brochure. GSK also added the phrase "For more information, visit MyAlli.com". These changes are acceptable.

3. On the carton labeling of the Refill Pack, under "The Refill Pack includes", delete the phrase "The Starter Pack contains additional guides and tools which will help you be more successful as you begin the Alli program."

FDA's Response: GSK made this change and it is acceptable.

The Refill Pack label (PDP, top and side panels) is acceptable with one exception: the parts of the label that are printed in light grey should be made darker to enhance readability. This can be done at the next printing.

B. Starter Pack and Refill Carton Labeling/Drug Facts

4. Under ***Warnings***, under **When using this product**, under the second bulleted statement, delete the third sentence which reads [redacted]

FDA's Response: GSK made this change to the Starter Pack and the Refill Pack and it is acceptable.

5. Under ***Directions***, revise the first bulleted statement to read "read the enclosed brochure for other important information".

FDA's Response: GSK made this change to the Starter Pack and the Refill pack and it is acceptable.

6. Under ***Directions***, revise the first sentence of the fifth bulleted statement to read: "use with a reduced-calorie, low-fat diet and exercise program until you reach your weight loss goal."

FDA's Response: GSK made this change to the Starter Pack and the Refill Pack and it is acceptable.

C. Bottle Label (60, 90, 120ct)

7. Delete the bulleted statement that reads [redacted]

FDA's Response: GSK made this change and it is acceptable. The bottle labels are acceptable with one exception: FDA recommends that the gray font be darkened at the next printing for readability.

D. Read Me First/Keys to successful weight loss

8. Under "Keys to successful weight loss", delete the sentence that reads [redacted]

FDA's Response: GSK made this change that it is acceptable.

9. Under "Use Alli as directed", delete the phrase [redacted]

FDA's Response: GSK made this change and it is acceptable.

10. In the Read Me First (Keys to successful weight loss) brochure, under "Eat right", under "**Choose foods low in fat; reduce calories and portion sizes**",

revise the phrase that reads [redacted] to "You can design your own menus from scratch, or use planned weekly menus such as the menus found on **www.MyAlli.com.**"

FDA's Response: GSK made this change and it is acceptable. At the next printing, GSK could change the part of the phrase that reads "on **MyAlli.com** to "at **MyAlli.com**".

11. Under "Write it down", revise the sentence which begins [redacted] to "**Keep a daily journal with you every day...**".

FDA's Response: GSK made this change and it is acceptable.

Reviewers Recommendations

The following comments may be conveyed to the sponsor.

GSK asked FDA to refer to GSK's submission of January 17, 2007 for the text and graphic specifications used in the Drug Facts portion of the Starter Pack and Refill carton. The font and graphic specifications are acceptable and in accordance with 21 CFR 201.66.

The Starter Pack labeling (60, 90, 120ct) (PDP, Top, Drug Facts) is acceptable.

The Refill carton labeling (120ct) (PDP, Side, Drug Facts) is acceptable.

The bottle label (60, 90, 120ct) is acceptable.

The Read Me First brochure is acceptable.

At the next printing, FDA recommends that GSK darken the gray print on the Starter Pack (PDP, top panel), Refill carton (PDP, side panel) and bottle labels for enhanced readability. Also, at the next printing, in the Read Me First brochure, under "Eat Right", under "Choose foods low in fat; reduce calories and portion sizes", GSK could change the part of the phrase that reads "on **MyAlli.com** to "at **MyAlli.com**" for consistency with the carton labeling.

Arlene Solbeck, MS
Senior Regulatory Review Scientist
Division of Nonprescription Regulation Development

Helen Cothran, BS
Team Leader
Division of Nonprescription Regulation Development

NDA 21-887
HFD-510: Parksl/Colman/Golden/Mele/Sahlroot/Rosebraugh
ONP: Division File
ONP: Ganley/Segal/Solbeck/Cothran/Feibus/Weiss/Olin/Shetty/Schiffenbauer/Nikhar
DOCID: 2_02_07OrlistatLabelReview.doc

13 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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/s/

Arlene Solbeck
2/5/2007 11:09:48 AM
INTERDISCIPLINARY

Helen Cothran
2/5/2007 12:15:48 PM
INTERDISCIPLINARY

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

EMAIL TRANSMITTAL SHEET

DATE: January 31, 2007

To: Erin Oliver Regulatory Affairs	**From:** Keith Olin, R.Ph. Regulatory Project Manager
Company: GlaxoSmithKline	Division of nonprescription Clinical Evaluation
Email Address: Erin.E.Oliver@gsk.com	**Fax number:** (301)796-9899
Phone number: 973-889-2516	**Phone number:** (301) 796-0962

Subject: Alli – Label Comments

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☑ NO

Please refer to your new drug application dated August 4, 2006, received August 7, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alli (60 mg Orlistat) tablets. We also refer to your January 17, 2007, submission containing revised draft labeling in response to our email dated January 12, 2007.

In connection with our review of the labeling section of your application, we have the following comments and requests:

Refill Pack:

1. Place the Read Me First/Keys to successful weight loss brochure in the Refill Pack.

Refill Carton Label:

2. On the carton label, under "The Refill Pack includes", add reference to the Read Me First brochure.

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed above as soon as possible, as an amendment to your NDA. If you have any questions, contact Keith Olin, Regulatory Project Manager at (301) 796-0962.

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/s/

Keith Olin
1/31/2007 06:04:51 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

EMAIL TRANSMITTAL SHEET

DATE: January 30, 2007

To: Erin Oliver Regulatory Affairs	**From:** Keith Olin, R.Ph. Regulatory Project Manager
Company: GlaxoSmithKline	Division of nonprescription Clinical Evaluation
Email Address: Erin.E.Oliver@gsk.com	**Fax number:** (301)796-9899
Phone number: 973-889-2516	**Phone number:** (301) 796-0962

Subject: Alli – Label Comments

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☑ NO

Please refer to your new drug application dated August 4, 2006, received August 7, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alli (60 mg Orlistat) tablets. We also refer to your January 17, 2007, submission containing revised draft labeling in response to our email dated January 12, 2007.

In connection with our review of the labeling section of your application, we have the following comments and requests:

Starter Pack and Refill Pack Carton Label

1. On the top panel of the Starter Pack, under "*The Starter Pack includes*:", delete reference to the Welcome Guide, Companion Guide, QuickFacts Cards, Healthy Eating Guide, Calorie & Fat Counter, and Daily Journal. It is acceptable to add, in their place, a phrase such as "For more information, visit www.MyAlli.com", which is similar to a statement under the **Drug Facts** box which reads "For more information and to learn more about Alli, visit us at www.MyAlli.com."

2. On the carton labeling of the Refill Pack under "The Refill Pack includes", delete reference to the Companion Guide.

3. On the carton labeling of the Refill Pack, under "The Refill Pack includes", delete the phrase "The Starter Pack contains additional guides and tools which will help you be more successful as you begin the Alli program."

Starter Pack and Refill Pack ***Drug Facts***

4. Delete the third sentence, under the heading ***When using this product***, under the second bulleted statement which reads "See enclosed materials for tips on how to follow a well-balanced, reduced-calorie, low-fat diet."

5. Revise the first bulleted statement under the heading ***Directions***, to read "read the enclosed brochure for other important information".

6. Revise the first sentence of the fifth bulleted statement under the heading ***Direction***s to read: "use with a reduced-calorie, low-fat diet and exercise program until you reach your weight loss goal."

Starter Pack and Refill Pack Bottle Label

7. Bottle label (60, 90, and 120 ct): delete the bulleted statement that reads

Read Me First (Keys to successful weight loss) Brochure:

8. Delete the sentence under "Keys to successful weight loss" that reads "See the inside cover of the *Welcome Guide (Hi)* to learn more."

9. Under "Use Alli as directed", delete the phrase "and other materials in your Starter Pack".

10. Under "Eat right", under "**Choose foods low in fat; reduce calories and portion sizes**", revise the phrase that reads [redacted] to "You can design your own menus from scratch, or use planned weekly menus such as the menus found on **www.MyAlli.com**."

11. Under "Write it down", revise the sentence which begins [redacted] to "**Keep a daily journal with you every day**...".

The only materials that we are considering as part of the labeling that we will approve are the carton and ***Drug Facts*** label, the bottle label, and the Read Me First/Keys to successful weight loss brochure. The other supporting materials (Companion Guide, Daily Journal, QuickFacts Card, Healthy Eating Guide, Calorie & Fat Counter, and Welcome Guide) will not be considered as part of the labeling that we will approve and cannot be mentioned or referenced in the approved labeling.

You can choose other ways to disseminate the supporting materials, either in the box or via phone or web with a number or address on the box.

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed above as soon as possible, as an amendment to your NDA. If you have any questions, contact Keith Olin, Regulatory Project Manager at (301) 796-0962.

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

/s/

Keith Olin
1/30/2007 01:13:50 PM
CSO

OTC Drug Labeling Review

Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#:	**21-887**
Submission Date:	January 17, 2007
Type of Submission:	Original New Drug Application/BF
Sponsor:	GlaxoSmithKline
Drug Product:	Orlistat OTC
Active Ingredient:	•Orlistat, 60 mg in each capsule
Indication:	•promotes weight loss in overweight adults when used along with a reduced calorie and low fat diet
Stock Keeping Units:	4 (60 capsule starter pack, 90 capsule starter pack, 120 capsule starter pack, 120 capsule refill pack)
Review Date:	January 31, 2007
Reviewer:	Arlene Solbeck Division of Nonprescription Regulation Development
Project Manager:	Keith Olin Division of Nonprescription Clinical Evaluation

Background

Orlistat is a pancreatic lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. Hoffmann-La Roche, Inc. first submitted an investigational new drug application (IND 31,617) for orlistat capsules in May, 1988.

On April 23, 1999, FDA approved NDA 20-766 for the prescription-only marketing of Xenical®, orlistat 120 mg tid. FDA approved a pediatric indication for ages 12-16 on June 12, 2004.

On June 19, 2001, FDA received a Hoffman-La Roche, Inc. application for IND 62,758 to investigate the development of orlistat for OTC marketing. In September 2004, GSK acquired ownership of IND 62,758 from Hoffman-La Roche, Inc. GSK has right of reference to relevant information within IND 31,617 and NDA 20-766, but the ownership of and responsibility for these two applications remain with Roche.

OTC Orlistat Timeline:

- On June 6, 2005 GSK submitted NDA application 21-887 for OTC marketing of 60 mg orlistat capsules tid.
- On January 24, 2006 the Nonprescription Drugs and the Endocrine and Metabolic Drugs Advisory Committees met to discuss the safety and efficacy of OTC use of orlistat.
- FDA issued an approvable letter (AE) on April 6, 2006 to GSK.
- On April 13, 2006 GSK submitted an official request for an end-of-review meeting with FDA. A briefing document, containing a specific list of questions for discussion, was received on May 17, 2006.
- FDA sent answers to the questions to GSK on June 9, 2006.
- GSK and FDA met on June 14, 2006 to discuss specific issues related to the design of GSK's proposed label comprehension and self-selection study protocols, and also revised labeling for OTC marketing of orlistat.
- On August 4, 2006, GSK resubmitted NDA 21-877 in response to FDA's approvable letter.
- On December 22, 2006, some labeling comments were faxed to GSK.
- On January 9, 2007, GSK and FDA participated in a labeling discussion via T-con, in response to FDA's December 22, 2006 fax. More labeling comments were emailed to GSK on January 12, 2007.
- GSK's revised labeling, which constituted a complete response to FDA's December 22, 2006 labeling review, and revisions requested by FDA in January 2007, was received on January 17, 2007.
- FDA requested revised labeling from GSK on January 25, 2007.
- GSK responded to FDA on January 30, 2007 with a question about one of FDA's recommendations in the January 25th request.

This label review is an addendum to FDA's January 25th label review to answer GSK's question.

GSK's Question

On January 25, 2007, FDA requested, among others, the following labeling revisions:

- "Starter and Refill Pack: under **Drug Facts**, under ***Directions***, revise the first bulleted statement to read "read the enclosed brochure for other important information".

- "On the carton labeling of the Refill Pack under "The Refill Pack includes", delete reference to the Companion Guide."

GSK contacted FDA and stated that if they deleted reference to the Companion Guide on the Refill Pack, then there would be no brochure in the carton for the first bulleted statement under ***Directions*** (which would state "read the enclosed brochure for other important information") to refer to. They asked FDA if they should delete that first bulleted statement in **Drug Facts** under ***Directions*** on the Refill Pack.

Reviewers Recommendations

The following comments may be conveyed to the sponsor: Regarding the Refill Pack, since reference to the Companion Guide must be deleted because it is not part of the official product labeling:

1. Keep the first bulleted statement in **Drug Facts** under ***Directions*** which reads "read the enclosed brochure for other important information".

2. Put the Read Me First/Keys to successful weight loss brochure in the Refill Pack for the statement to refer to.

3. On the carton under "The Refill Pack includes", add reference to the Read Me First brochure.

Arlene Solbeck, MS
Senior Regulatory Review Scientist
Division of Nonprescription Regulation Development

Helen Cothran, BS
Team Leader
Division of Nonprescription Regulation Development

NDA 21-877
HFD-510: Parksl/Colman/Golden/Mele/Sahlroot/Rosebraugh
ONP: Division File
ONP: Ganley/Segal/Solbeck/Cothran/Feibus/Weiss/Olin/Shetty/Schiffenbauer/Nikhar
DOCID: 1_31_07OrlistatLabelReview.doc

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/s/

Arlene Solbeck
1/31/2007 02:00:28 PM
INTERDISCIPLINARY

Helen Cothran
1/31/2007 02:13:29 PM
INTERDISCIPLINARY

OTC Drug Labeling Review

Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#:	**21-887**
Submission Date:	January 9, 2007
Type of Submission:	Fax
Sponsor:	GlaxoSmithKline
Drug Product:	Orlistat OTC
Active Ingredient:	•Orlistat, 60 mg in each capsule
Indication:	•promotes weight loss in overweight adults when used along with a reduced calorie and low fat diet
Stock Keeping Units:	4 (60 capsule starter pack, 90 capsule starter pack, 120 capsule starter pack, 120 capsule refill pack)
Review Date:	January 10, 2007
Reviewer:	Arlene Solbeck Division of Nonprescription Regulation Development
Project Manager:	Keith Olin Division of Nonprescription Clinical Evaluation

I. Background

In reference to GSK's new drug application dated August 4, 2006 for 60 mg OTC orlistat capsules, ONP sent GSK a fax on December 22, 2006 with labeling comments. GSK was asked to submit revised draft labeling. On January 9, 2007, GSK and ONP participated in a labeling discussion via T-con, in response to a fax submitted to ONP by GSK with some labeling revisions. This fax does not constitute GSK's official revised labeling submission as requested by ONP. However, ONP agreed to respond to GSK

with any additional comments regarding their revised faxed label (Drug Facts and bottle labels). The following are the remaining deficiencies and recommendations for the Drug Facts and bottle labels that are in addition to those discussed in the T-con.

II. Recommendations

A. Drug Facts

1. Remove the dots that connect the subheadings ***Active ingredient*** and ***Purpose***.

2. Put a period after the pregnancy and breast-feeding warning.

3. Under ***Directions***, bold the first sentence of bullet #3 "**for overweight adults 18 years and older:**" so it stands out.

4. Under ***Directions***, revise the second sub-bullet under "**for overweight adults 18 years and older:**" to read "do not take more than 3 capsules daily" (i.e., change ——— to "take more than").

5. Under ***Directions***, revise the sixth bulleted statement to read "if you stop taking orlistat, continue with your diet and exercise program" (i.e., substitute the word "taking" for the word ———

6. Under ***Directions***, revise the seventh bulleted statement to read: "if you start to regain weight after you stop taking orlistat, you may need to start taking orlistat again along with your diet and exercise program" (i.e., change ———' to "start" and add the word "again").

B. Bottle

7. In the subheading "**Ask a doctor before use if you have ever had**", unbold the words "ever had" to be consistent with Drug Facts.

8. In the subheading "**Other Information**", change the capital letter "I" in "Information" to a small letter "i" to be consistent with Drug Facts.

1/10/07

Arlene Solbeck, MS
Senior Regulatory Review Scientist
Division of Nonprescription Regulation Development

1/10/07

Helen Cothran, BS
Team Leader
Division of Nonprescription Regulation Development

2 Page(s) Withheld

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

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/s/

Arlene Solbeck
1/11/2007 07:58:37 AM
INTERDISCIPLINARY

Helen Cothran
1/11/2007 10:21:56 AM
INTERDISCIPLINARY

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

EMAIL TRANSMITTAL SHEET

DATE: December 22, 2006

To: Erin Oliver Regulatory Affairs	**From:** Keith Olin, R.Ph. Regulatory Project Manager
Company: GlaxoSmithKline	Division of nonprescription Clinical Evaluation
Email Address: Erin.E.Oliver@gsk.com	**Fax number:** (301)796-9899
Phone number: 973 889-2516	**Phone number:** (301) 796-0962

Subject: NDA 21-887 – Labeling Comments

Total no. of pages including cover: 9

Document to be mailed: ☐ YES ☑ NO

Please refer to your new drug application dated August 4, 2006, received August 7, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alli (60 mg orlistat) tablets. We have the following deficiencies and recommendations.

Submit draft labeling revised as follows:

I. Starter Pack (60, 90, 120ct) and Refill Pack (120ct)

A. Principal Display Panel (PDP) (60, 90, 120ct)/Top Panel

1. Delete the promotional statement

B. Back Panel (Drug Facts)

2. Under the heading **Use**, delete the period at the end of the bulleted statement "for weight loss in overweight adults, 18 years and older, when used along with a reduced calorie and low fat diet".

3. Under the heading **Use**, revise "reduced calorie and low fat diet" to read "reduced-calorie and low-fat diet". Note the use of the hyphens in "reduced-calorie" and "low-fat".

4. Under the heading **Warnings**, under the subheading **Allergy alert**, add a colon after the word "alert".

5. Under the heading **Warnings**, under the subheading "**Do not use**", bold the first bulleted statement "if you are taking cyclosporine".

6. Under the heading **Warnings**, under the subheading "**Ask a doctor before use if you are**", combine the first and second bulleted statements to read: "**taking warfarin (blood thinning medicine)**, or taking medicine for diabetes or thyroid disease. Your medication dose may need to be adjusted."

7. Under the heading **Warnings,** under the subheading "**When using this product**", revise the first sentence in the first bulleted statement to read "**take a multivitamin once a day, at bedtime.**"

8. Under the heading **Warnings**, under the subheading "**When using this product**", revise the second bulleted statement to read "follow a well-balanced, reduced-calorie, low-fat diet. Try starting this diet before taking orlistat.
t.

9. Under the heading **Warnings,** under the subheading "**When using this product**", combine the proposed third and fourth bulleted statements into one bulleted statement (which becomes the third bulleted statement under **When using this product**) to

read: "orlistat works by preventing the absorption of some of the fat you eat. The fat passes out of your body, so you may have bowel changes. You may get : [bullet] gas with oily spotting [bullet] loose stools [bullet] more frequent stools that may be hard to control".

10. Under the heading **Warning,** under the subheading "**When using this product**", shorten the proposed fifth bulleted statement "[redacted] to "eating a low-fat diet lowers the chance of these bowel changes". This becomes fourth bulleted statement under **When using this product**.

11. Under the heading **Warnings,** under the subheading "**When using this product**", combine the proposed sixth and seventh bulleted statements, which becomes the fifth bulleted statement under "**When using this product**", to read "for every 5 pounds you lose from diet alone, orlistat can help you lose 2-3 pounds more". In studies, most people lost 5-10 pounds over 6 months."

12. Under the heading **Warnings**, under the "overdose" warnings, delete the word [redacted]

13. Under the heading **Directions**, take the last bulleted statement which reads [redacted] and move it up to be the first bulleted statement. Revise the statement by deleting the words, [redacted] The proposed first bulleted statement, "for overweight adults 18 years and older", will become the fourth bulleted statement under **Directions** (see #16 below).

14. Under the heading **Directions**, revise the second bulleted statement about diet and exercise to read: "diet and exercise are the starting points for any weight loss program. Try these first before adding orlistat. Then, add a third sentence to read: "Check with your doctor before starting any exercise program."

15. Because we think the BMI chart belongs in the **Directions** section of **Drug Facts** rather than under the heading **Other information**, move the BMI chart to the **Directions** section and make the third bulleted statement under **Directions** read as follows: "[bullet] to see if orlistat capsules are right for you, find your height on the chart to the right. You should only start a weight loss program with orlistat if your weight is the same or more than the weight shown for your height."

16. Under the heading **Directions**, make the fourth bulleted statement read as follows: "for overweight adults 18 years and older:" Then, your current bullets 3 and 4 can follow as sub-bullets under bullet 4 as follows:

- for overweight adults 18 years and older:
- take 1 capsule with each meal containing fat
- do not exceed 3 capsules daily

17. Revise the fifth bulleted statement under the heading **Directions** to read: "use with a reduced-calorie, low-fat diet until you reach your weight loss goal. Most weight loss occurs in the first 6 months."

18. Revise the seventh bulleted statement under the heading **Directions** to read: "if you start to regain weight after you stop taking orlistat, you may need to —— taking orlistat along with you diet and exercise program".

19. Revise the multivitamin statement under the heading **Directions** (the eighth bulleted statement) to read "**take a multivitamin once a day, at bedtime, when using orlistat**".

20. Under the heading **Other information**, because FDA believes that the BMI chart and instructions on how to use the BMI chart should be moved to the **Directions** section, and since the third bulleted statement about diet and exercise is redundant and can be deleted, the only two bullets remaining in **Other information** will be the storage information (bulleted statements 1 and 2). In addition, revise bullet #2 to read: "protect drug from excessive light, humidity and temperatures over 30°C (86°F).

21. Revise bullet size (for all bulleted statements in ***Drug Facts***) to 5-point type size to be in accordance with 21 CFR 201.66 (d)(4).

22. Under the ***Drug Fact*** box, we recommend revising the statement which begins [———————————————] to "To get information in Spanish.....". We think that having the word "information" in the sentence might be useful to Spanish consumers who might not understand English well but might recognize the word "information".

We have included a mockup of the revisions that FDA is requesting for ***Drug Facts*** which can be found in Table 1. Please remember that this mockup is for content purposes only. The font sizes for title, headings, subheadings, condensed text, bullets and other graphic features must be in accordance with 21 CFR 201.66.

II. Bottle (60, 90, 120ct)

23. Revise bottle label to be consistent with the changes being made to the ***Drug Facts*** labels of the starter and refill packs. We have included a mockup of a bottle label with the suggested revisions for your convenience. This is located in Table 2.

III. Read Me First (Keys to successful weight loss)

24. Delete all page references to the Companion Guide and/or the Healthy Eating Guide. These are not considered part of FDA's approved labeling for orlistat.

25. Under "Use Alli as directed", insert the words "Drug Facts" before the word "label".

26. Under "Expect steady, gradual weight loss":

a. Revise the first sentence to read "Set realistic goals that result in steady gradual weight loss".

b. Revise the expectation of benefit statement to read: [redacted]

c. Replace the words [redacted] in the second paragraph with "reduced-calorie, low-fat diet."

27. Under "Eat right", delete the paragraph which begins "Choose foods low in fat." but keep the subtitle. Make it part of the subtitle of the next paragraph (i.e., "**Choose foods low in fat; reduce calories and portion sizes**. While choosing low-fat foods.....").

28. Under "Write it down", revise the first sentence to read "It is important for your weight loss success to record what you eat and drink."

29. Under "Stick to your program", delete [redacted] from the third sentence which reads "Don't expect [redacted] to follow your program....".

IV. Supporting Materials

Although the rest of the supporting materials were not tested for label comprehension and are not considered labeling, FDA has the following comments about some of the supporting materials:

[redacted]

These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. In order to ensure a timely action for this new drug application,

we request that you respond to the issues listed above as soon as possible, as an amendment to your NDA. If you have any questions, contact Keith Olin, Regulatory Project Manager at (301) 796-0962.

Attached Labeling:

3 Page(s) Withheld

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✓ Draft Labeling

_____ Deliberative Process

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/s/

Keith Olin
12/22/2006 01:01:50 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-887

GalxoSmithKline Consumer Healthcare, L.P.
Attention: Erin Oliver
Assistant Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054

Dear Ms. Oliver:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alli (60 mg Orlistat) capsules.

We also refer to the meeting between representatives of your firm and the FDA on June 14, 2006. The purpose of the meeting was to provide guidance on specific issues related to the design of the proposed label comprehension and self-selection study protocols for NDA 21-887, Alli (60 mg Orlistat) capsules..

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 Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEMORANDUM

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

SUBJECT: **Meeting Minutes: Discussion of the label comprehension studies and self selection protocols**

MEETING DATE: June 14, 2006
TIME: 4:00 to 5:00 PM EST
LOCATION: White Oak Campus, Building 22
APPLICATION: NDA 21-887
DRUG NAME: Alli (orlistat) Capsules
TYPE OF MEETING: Guidance Meeting

MEETING RECORDER: Keith Olin

FDA ATTENDEES:

CDER Participants:

Division of Nonprescription Clinical Evaluation

Andrea Leonard-Segal, M.D.	Director
Karen Feibus, M.D.	Acting Clinical Team Leader
Linda Hu, M.D.	Medical Officer
Susanna Weiss, Ph.D., J.D.	Social Science Analyst
Keith Olin, R.Ph.	Regulatory Project Manager

Division of Nonprescription Regulation Development

Helen Cothran, B.S.	Interdisciplinary Scientist Team Leader
Arlene Solbeck, M.S.	Senior Regulatory Review Scientist

EXTERNAL CONSTITUENT ATTENDEES:

GlaxoSmithKline

David Schifkovitz	Director, Regulatory Affairs
George Quesnelle	President, Consumer Healthcare North America
John Dent	GSK Consultant (retired Sr. Vice President, Research and Development, GSK)
Steve Burton	Vice President, Weight Control Business Unit
Randy Koslo	Director, Medical Affairs

Vidhu Bansal	Director, Medical Affairs
Cecilia Hale	Senior Statistician, Biostatistics and Data Management
Andrea Harkins	Senior Consumer Research Manager
Erin Oliver	Associate Director, Regulatory Affairs
Susan Schwartz	Director, New Product Research

BACKGROUND:

On June 6, 2005, GSK submitted a new drug application (NDA 21-887) for Alli (orlistat), 60 mg Capsules, seeking approval for over-the-counter use. The FDA issued an approvable (AE) letter on April 6, 2006.

On April 13, 2006, GSK submitted an official request for an end-of-review meeting with the Agency to discuss the deficiencies listed in the April 6, 2006 letter. A meeting package, dated May 17, 2006, containing a specific list of questions for discussion was also received from GSK. Prelimimary responses to the questions were sent to GSK on June 9, 2006.

Based on the preliminary responses, GSK revised the labeling for the Alli product. These labeling revisions and other issues were discussed with GSK at the end of review meeting on June 14, 2006 with the Division of Metabolism and Endocrinology Products and the Division of Nonprescription Clinical Evaluation.

A second meeting was held later that same day at the request of GSK between GSK and the Division of Nonprescription Clinical Evaluation to discuss specific issues related to the design of the proposed label comprehension and self-selection study protocols.

MEETING OBJECTIVES:
To provide guidance on specific issues related to the design of the proposed label comprehension and self-selection study protocols for NDA 21-887, Alli (60 mg Orlistat) capsules.

GENERAL DISCUSSION:
Following introductions and a brief discussion of the purpose of the meeting, discussion focused on Questions 3 and 4 from the May 17, 2006 meeting package. Preliminary responses to the questions were sent to GSK on June 9, 2006. These preliminary responses did not change based on discussions that occurred at the June 14, 2006 meeting and appear below in italics. A summary of any additional discussion follows each preliminary comment.

QUESTIONS:

3. **Does the agency agree with the protocol design and associated questionnaire to be used in Label Comprehension testing?**

   Agency Response:

   A. *There is a need for additional questions that more accurately and comprehensively test distinct pieces of information in the label. We would like to be reassured that consumers have assimilated each of the label concepts listed below. Ideally, each question should address one concept (one cognitive step) at a time.*

   - *Product Use and Target Population*
     - *That the medication is only one part of a complete weight loss program.*
     - *The age restriction for product use (i.e., it is for adults/18 years and older).*
     - *The ability to read the height and weight chart.*

   - *Multivitamin Use*
     - *When using orlistat, do you need to take anything else?*
     - *How often do you need to take the multivitamin?*
     - *When should you take the multivitamin?*

   - *Side Effects*
     - *Do consumers understand that orlistat use may cause unpleasant changes in bowel habits if they do not reduce the amount of fat in their diets?*

   - *Duration of Use*
     - *When should a consumer stop taking orlistat?*
     - *When a consumer decides to stop using orlistat, is there anything else he/she should do?*
     - *What should a consumer do if he/she stops using orlistat and begins to regain lost weight?*

Additional Discussion:
FDA explained to GSK that it would be unnecessary to retest the "Product Use and Target Population" issues. However GSK must retest "Multivitamin Use" to ensure that consumers understand (1) how often they need to take a multivitamin, and (2) when they should take a multivitamin (e.g., away from a meal).

FDA further explained that GSK would not need to retest the "Duration of Use" issues that were listed in the draft comments. However, the points outlined in the draft comments should be clearly reflected in the revised drug facts label.

   B. *We have some reservations and questions regarding the answer choices that might be coded as correct or acceptable. For each question, describe exactly which responses in the interviewer's sheets will be coded as correct and which will be coded as acceptable so that we can determine if we agree with you.*

Additional Discussion:
FDA requested that GSK describe exactly which responses in the interviewers' sheets will be coded as CORRECT and which will be coded as ACCEPTABLE. GSK described their coding principles as follows: CORRECT equals verbatim wording as written in the label. ACCEPTABLE may not necessarily be verbatim repetition but it would be a very close paraphrase of the label in consumer friendly language.

FDA emphasized that an ACCEPTABLE response must capture all of the learning objectives of a particular label instruction that is being tested. Although a respondent's own words can differ slightly from the precise label language, the response must reflect the complete instructional intent of the label language, and must be functionally equivalent in meaning to the label instruction that is being tested. FDA cited a specific example on page 106, card D, Protocol W2900425, concerning the way in which the response related to the timing for taking a multivitamin would be coded. FDA asked GSK how they would code a response that said "once a day". GSK explained that they would do a follow up probing question to try to obtain more information about the timing for take the multivitamin, and if the response was, for example "at bedtime" or "last thing at night," those answers would be coded as acceptable.

C. *We do not agree with the question format and content proposed for testing comprehension of the new package insert Read Me First: Keys to Successful Weight Loss. The use of scenarios as proposed in your draft study will bias the study results because:*
   - *Too much information is disclosed*
   - *Some scenarios are too general and simplistic*
   - *The "FOLLOW"/ "NOT FOLLOW" answers are too limited (50/50 chance of answering correctly)*

   Rewrite your scenarios to avoid biasing the study results. You may also consider introducing some simple questions with open-ended responses.

Additional Discussion:
FDA gave an example of a scenario on page 107, which was considered too simplistic and too easy for respondents to give the correct answer. GSK said they understood the FDA's concern and would rewrite the scenarios and questions to make them less simplistic so it would be less easy to guess the correct response.

4. Does the agency agree with the protocol design and associated questionnaire to be used in cyclosporine self-selection testing?

Agency Response:

- *The following statement in the flyer used for recruitment can bias results of the self-selection study and should be deleted:* ***It is important that the information on the label is correctly understood by the consumer so they can decide for themselves whether the product is appropriate to use.*** *This statement cues subjects to more closely examine the label for the proper self-selection criteria.*

Additional Discussion:
GSK explained that it was difficult to get organ transplant centers to agree to participate in the study. Part of the process to obtain agreement meant that GSK would have to explain very precisely what the study would involve and what consumers would be asked to do. This is why the recruitment flyer used such specific wording. Based upon GSK's explanation, FDA acknowledged that the wording in the flyers would not need to be revised.

- *The self selection question should read:* ***Is this product appropriate for you to use.*** *The phrase,* ***Based on what you read****, prompts the participant to re-examine the label more closely and does not simulate an actual self-selection situation.*

Additional Discussion:
FDA emphasized that it was not appropriate for the study script to keep reminding the participants to read the label, nor would it be appropriate to ask participants the question "based on what you read . . . ," since this prompts participants to read the label more carefully than they would in a real-life situation and does not properly simulate an actual use situation. GSK agreed to remove the "based on what you read" prompt.

- *On page 25 of the self-selection protocol, it is appropriate to ask subjects to read the label and to tell them that they will be able to refer to the label during the survey. However, prompting participants to read the* ***entire*** *label, to refer to the label* ***as often as they would like****, and to* ***not guess at the answers but instead refer to the label****, does not simulate a "real-life" situation and may bias your results.*

Additional Discussion:
FDA stated that it is not appropriate to repeatedly ask subjects to read the label and tell them they will be able to refer back to the label during testing. Prompting participants to *read the entire label and to refer to the label as often as they would like, and not guess the answers,* does not reflect a real-life situation and would bias the study results. FDA emphasized that in real-life situations, self-selection decisions are usually made in just a few minutes without any constant reminders to read the label. GSK agreed to remove the redundant reminders to refer to the label.

- *The confidentiality disclosure and study participation agreement form should be free of bias.*

- *On page 66 of your submission (page 28 of the self-selection protocol), question 11 should be asked before question 10 to avoid biasing subject response.*

Additional Discussion:
FDA rescinded this request after hearing the explanation provided by GSK. GSK said that the order of these questions was intentional, in order to determine: (1) if the subject saw the label warning (question 10), and (2) if the subject did not see the warning, they were prompted to refer back to the label and answer whether the product was appropriate for them to take (question 11).

- *Submit information you may have on concomitant use of orlistat and other immunosuppressant drugs. Does orlistat reduce the absorption of other lipid-soluble immunosuppressant drugs such as tacrolimus?*

There was no additional discussion regarding this response.

AGREEMENTS AND ACTION ITEMS:
1) GlaxoSmithKline agreed to review and revise, where needed, their label comprehension and self-selection study protocols based on the discussion from this meeting.

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/s/

Keith Olin
11/1/2006 03:35:53 PM
CSO

Andrea Segal
11/3/2006 10:03:51 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products

EMAIL TRANSMITTAL SHEET

DATE: October 16, 2006

To: Erin Oliver Regulatory Affairs	**From:** Keith Olin, R.Ph. Regulatory Project Manager
Company: GlaxoSmithKline Consumer Healthcare	Division of nonprescription Clinical Evaluation
Email Address: Erin.E.Oliver@gsk.com	**Fax number:** (301)796-9899
Phone number: (973) 889-2516	**Phone number:** (301) 796-0962

Subject: Information Request – NDA 21-887

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☑ NO

Please refer to your new drug application dated August 4, 2006, received August 7, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alli (60 mg Orlistat) tablets. In connection with our review of NDA 21-887, we have the following requests:

1. Please provide a Table indicating the following information concerning MULTIVITAMIN instructions:

A. How many subjects (reported as GP and LL "n" and "%") answered ALL THREE elements of the multivitamin instruction (need to take a multivitamin; need to take it daily; need to take it at bedtime) CORRECTLY?

B. How many subjects (reported as GP and LL "n" and "%") answered 2 out of the 3 elements correctly, and indicate which elements they answered correctly.

C. How many subjects (reported as GP and LL "n" and "%") answered only 1 (ONE) element correctly, and indicate which element was answered correctly.

D. How many subjects (reported as GP and LL "n" and "%") answered ALL THREE elements of the multivitamin instruction INCORRECTLY?

2. Please provide a table that summarizes demographic information in a Table as follows:

Demographic Breakdown	General Population N %	Low Literacy Group N %
Gender		
Male		
Female		
Age		
18-24		
25-29		
30-39		
40-49		
50-59		
60+		
Race/Ethnicity		
Caucasian (non-Hispanic)		
African American (non-Hispanic)		
Hispanic		
Asian		
Native American		
Other		
Missing		

3. **Please provide additional demographic information in a Table as follows:**

City, State	Number of interviews	Mean Household Income of Mall Shoppers	Mean Number of Years in School/College of Mall Shoppers
Duluth, MN	25		
Springfield, MO	25		
Ft. Smith, AR	25		
Fredericksburg, VA	26		
Salina, KS	36		
Charleston, WV	26		
South Bend, IN	26		
Lakeland, FL	26		
Wayne, NJ	25		
Corpus Christi, TX	26		
San Francisco, CA	29		
Milwaukee, WI	28		
Atlanta, GA	26		
Boston, MA	26		
Seattle, WA	26		

4. **Please provide additional demographic information in a Table as follows:**

City, State	Number of interviews	Mean Household Income of Mall Shoppers	Mean Number of Years in School/College of Mall Shoppers
Baltimore, MD	34		
Los Angeles, CA	73		
Louisville, KY	10		

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed above as soon as possible, as an amendment to your NDA. If you have any questions, contact Keith Olin, Regulatory Project Manager at (301) 796-0962.

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/s/

Keith Olin
10/19/2006 03:35:42 PM
CSO

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
Assistant Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Oliver:

We acknowledge receipt on August 7, 2006 of your August 4, 2006 resubmission to your new drug application for Alli (orlistat) Capsules, 60 mg.

We consider this a complete, class 2 response to our April 6, 2006 action letter. Therefore, the user fee goal date is February 7, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the partial waiver (ages 0 – 11 years) and the deferral (ages 12 – 17 years) granted on August 18, 2005 for the pediatric study requirement for this application.

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

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology 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
8/22/2006 08:29:14 AM

OTC Drug Labeling Review

Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#:	**21-887**
Submission Date:	August 4, 2006
Type of Submission:	Original New Drug Application
Sponsor:	GlaxoSmithKline
Drug Product:	Orlistat OTC
Active Ingredient:	•Orlistat, 60 mg in each capsule
Indication:	•promotes weight loss in overweight adults when used along with a reduced calorie and low fat diet
Stock Keeping Units:	4 (60 capsule starter pack, 90 capsule starter pack, 120 capsule starter pack, 120 capsule refill pack)
Review Date:	December 20, 2006
Reviewer:	Arlene Solbeck Division of Nonprescription Regulation Development
Project Manager:	Keith Olin Division of Nonprescription Clinical Evaluation

Background

Orlistat is a pancreatic lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. Hoffmann-La Roche, Inc. first submitted an investigational new drug application (IND 31,617) for orlistat capsules in May, 1988.

On April 23, 1999, FDA approved NDA 20-766 for the prescription-only marketing of Xenical®, orlistat 120 mg tid. FDA approved a pediatric indication for ages 12-16 on June 12, 2004.

On June 19, 2001, FDA received a Hoffman-La Roche, Inc. application for IND 62,758 to investigate the development of orlistat for OTC marketing. In September 2004, GSK acquired ownership of IND 62,758 from Hoffman-La Roche, Inc. GSK has right of reference to relevant information within IND 31,617 and NDA 20-766, but the ownership of and responsibility for these two applications remain with Roche.

OTC Orlistat Timeline:

- On June 6, 2005 GSK submitted NDA application 21-887 for OTC marketing of 60 mg orlistat capsules tid.
- On January 24, 2006 the Nonprescription Drugs and the Endocrine and Metabolic Drugs Advisory Committees met to discuss the safety and efficacy of OTC use of orlistat. .
- FDA issued an approvable letter (AE) on April 6, 2006 to GSK.
- On April 13, 2006 GSK submitted an official request for an end-of-review meeting with FDA. A briefing document, containing a specific list of questions for discussion, was received on May 17, 2006.
- FDA sent answers to the questions to GSK on June 9, 2006.
- GSK and FDA met on June 14, 2006 to discuss specific issues related to the design of GSK's proposed label comprehension and self-selection study protocols, and also revised labeling for OTC marketing of orlistat.
- On August 4, 2006, GSK resubmitted NDA 21-877 in response to FDA's approvable letter.
- Initial labeling comments were faxed to the sponsor on December 22, 2006.

This current submission contains the following for review:

- Starter Pack Primary Display Panel (PDP), 60 count(ct)
- Starter Pack Back Panel (Drug Facts), 60ct
- Starter Pack PDP, 90ct
- Starter Pack Back Panel (Drug Facts), 90ct
- Starter Pack PDP, 120ct
- Starter Pack Back Panel (Drug Facts), 120ct
- Starter Pack Top Panel, 60ct
- Starter Pack Top Panel, 90ct
- Starter Pack Top Panel, 120ct
- Refill Pack, 120ct
- Bottle, 60ct
- Bottle, 90ct
- Bottle, 120ct
- Bottle Overwrap
- Companion Guide
- Companion Guide Refill

- Quick Facts
- Health Eating Guide
- Daily Journal
- Calorie Fat Counter.
- Welcome Guide
- Read Me First

Reviewers' Comments

FDA considers the "labeling" for this product to be the carton (all panels including Drug Facts), the bottle label, and the brochure "Read Me First". However, we will make comments to other parts of the sponsor's program brochures where applicable.

I. Starter Pack

A. Principal Display Panel (PDP) (60, 90, 120ct)/Top Panel

In the April 6, 2006 approvable letter, FDA made the following comments about the PDPs for the 60, 90, and 120ct starter packs. These comments were also discussed at the June 14, 2006 meeting between FDA and GSK.

- In the gold box with the words "Starter Pack", we recommend including the phrase "up to 20 day supply" for the 60 count, "up to 30 day supply" for the 90 count and "up to 40 day supply" for the 120 count cartons. Also, use a larger font.
- The phrase [redacted] should be revised to read "FDA approved non-prescription weight loss drug".

Sponsor's Response:

- The sponsor included the phrases "up to 20 day supply" for the 60 count, "up to 30 day supply" for the 90 count, and "up to 40 day supply" for the 120 count cartons. This is acceptable. The font size is also acceptable
- The sponsor revised the statement [redacted] to read "FDA approved non-prescription weight loss aid", for consistency with "Purpose" as it appears in the Drug Facts label. This is acceptable.
- The sponsor also added reference to the Read Me First Guide and the [redacted] to the top panel listing of package contents. This is acceptable.

FDA's Response: The PDPs for the 60, 90 and 120ct packages are acceptable as well as the top panels with one exception:

- Delete the promotional statement [redacted]

B. Back Panel (Drug Facts) (60,90,120ct)

In the April 6, 2006 approvable letter, FDA recommended that GSK make revisions to the Drug Facts labeling for various reasons. These recommendations were discussed further at the June 14, 2006 meeting between FDA and GSK. The revised labeling in this submission reflects revisions by the sponsor to these recommendations.

Purpose

1. Under ***Purpose***, GSK replaced the "L" in "Loss" and the "A" in "Aid" with small letters (i.e., "l" and "a") in accordance with 21 CFR 201.66(d)(1).

FDA's Response: These changes are acceptable.

Use

2. FDA recommended that GSK include statements in the labeling to send a clear message that diet and exercise should be tried before using orlistat, and that orlistat should be used in addition to diet and exercise. FDA advised GSK not to put all these statements in the ***Use*** section of Drug Facts to simplify the ***Use*** section. Therefore, in the ***Use*** section, GSK revised the statement from "promotes weight loss" to "for weight loss in overweight adults, 18 years and older, when used along with a reduced calorie and low fat diet." See also ***Other information*** (#11 below)

FDA's Response: This change is acceptable with two exceptions:

- Delete the period at the end of the bulleted statement "for weight loss in overweight adults, 18 years and older, when used along with a reduced calorie and low fat diet."
- Revise "reduced calorie and low fat diet" to read "reduced-calorie and low-fat diet". Note the use of the hyphens in "reduced-calorie" and "low-fat".

Warnings

3. Under ***Warnings***, FDA advised GSK to revise the labeling to help consumers understand that orlistat must not be used if a patient has an organ transplant or is receiving cyclosporine. GSK added an "**Organ transplant alert**" as the first warning under ***Warnings***. FDA advised GSK that we are not certain if yellow highlighting enhances comprehension of the highlighted text or whether highlighting positively or negatively affects comprehension of the remainder of the label. GSK's **Organ transplant alert** reads "[bullet] do not use if you have had an organ transplant. Orlistat interferes with the medicines used to prevent transplant rejection." The entire alert is highlighted in yellow.

   GSK also agreed to place a warning statement within the **Do not use** section of **Drug Facts** regarding cyclosporine (see below #5).

FDA's Response: The "**Organ transplant alert**" is acceptable. The highlighting is acceptable.

4. Under ***Warnings***, GSK added an allergy alert, which reads as follows: "**Allergy alert:** Do not use if you are allergic to any of the ingredients in orlistat capsules", in accordance with 21 CFR 201.66(c)(5)(ii)(B).

FDA's Response: this change is acceptable with one exception:

- Add a colon after the word "alert".

5. Under ***Warnings*** under "**Do not use**", FDA advised that GSK bold the first bulleted warning which starts "if you are taking cyclosporine....", and to add a second bolded sentence to that bullet which reads "**Orlistat decreases the amount of cyclosporine absorbed and this can cause organ rejection**." GSK added the first bulleted statement "if you are taking cyclosporine" and did not include the second bolded sentence to that bullet because the label now contains an **Organ transplant alert**. This was agreed upon at the June 14, 2006 meeting.

FDA's Response: GSK should bold the bulleted statement "if you are taking cyclosporine".

6. Under ***Warning***s under **Ask a doctor before use if you have**, FDA advised GSK to add pancreatitis, and to revise the warning because it seemed to suggest that consumers should only be concerned if they have these diagnoses now. The warning was revised to provide a message that people with a history of gallbladder problems, kidney stones, and pancreatitis should ask a doctor before use. The revised warning states: "**Ask a doctor before use if you have** ever had [bullet] gallbladder problems [bullet] kidney stones [bullet] pancreatitis".

FDA's Response: These changes are acceptable.

7. Under ***Warnings*** under "**Ask a doctor or pharmacist before use if you are**", FDA advised GSK to make the following revisions:
   - Make the second bulleted statement about warfarin the first bulleted statement. Then, add a second sentence to the bullet which reads [illegible] Bold both statements.
   - Revise the third bullet to read "taking other weight loss products".

FDA's Response: GSK made these revisions and the warning should be revised further as follows:

- Combine the first and second bullets about warfarin and diabetes and add thyroid disease to the list. The first bulleted statement should then read as follows: [bullet] **taking warfarin (blood thinning medicine)**, or taking medicine for diabetes or thyroid disease. Your medication dose may need to be adjusted." The third bulleted statement, "taking other weight loss

products", becomes the second bulleted statement under "**Ask a doctor or pharmacist before use if you are**".

8. Under ***Warnings*** under "**When using this product**", GSK made the following revisions:

- In FDA's April 6, 2006 approvable letter, FDA stated that it is important that GSK improve the labeling statement regarding vitamin use and test it in a label comprehension study. At the June 14, 2006 meeting, FDA also recommended that GSK add a statement that orlistat can reduce the absorption of some vitamins. GSK made the first bulleted statement under **When using this product** about multivitamin use which reads "**you need to take a multivitamin once daily, at bedtime**. Orlistat can reduce the absorption of some vitamins." The first statement is bolded and highlighted with yellow. A similar message is repeated in "***Directions***" (see # 11 below).

FDA's Response: Revise the first sentence of the multivitamin warning to read: "**take a multivitamin once a day, at bedtime**".

- GSK revised the second bullet in **When using this product** to read "to lose weight effectively, you must follow a well-balanced diet that is reduced in calories and contains 30% fat or less. You should try starting this diet before you begin taking orlistat capsules. See enclosed materials for information and tips on how to follow a well-balanced diet that is low in calories and fat."

FDA's Response: Simplify this warning by revising this bullet to read "follow a well-balanced, reduced-calorie, low-fat diet. Try starting this diet before taking orlistat. See enclosed materials for tips on how to follow a well-balanced, reduced-calorie, low-fat diet."

- GSK revised the third bulleted statement to state that the degree to which fat absorption is blocked has been revised from the previous "25 to 30%" to "25%" in accordance with the current one capsule dose.

FDA Response: Revise this bullet again to combine sponsor's third and fourth bulleted statements. See next response below.

- In the April 6, 2006 approvable letter, FDA stated that consumers should be aware of the most common adverse events leading to the discontinuation of use of orlistat. At the June 14, 2006 meeting, FDA also recommended including in the list of adverse events that bowel movements may be difficult to control. GSK revised the fourth bulleted statement under **When using this product**, about side effects of orlistat, to read "as a result of undigested fat passing through the body, you may experience bowel changes. Examples include loose and more frequent stools, gas with oily spotting, and urgent bowel movements."

FDA's Response: Revise this bullet to combine bullets three and four to read "orlistat works by preventing the absorption of some of the fat you eat. The fat passes out of your body, so you may have bowel changes. You may get: [bullet] gas with oily spotting [bullet] loose stools [bullet] more frequent stools that may be hard to control". This combines the sponsor's third and fourth bulleted statements into one bulleted statement (which becomes the third bulleted statement under **When using this product**). The sponsor's fifth bulleted statement "these bowel changes are related to how the product works. You can decrease the likelihood of these effects by reducing the fat in your diet." can be shortened to "eating a low-fat diet lowers the chance of having these bowel changes". This becomes the fourth bulleted statement under **When using this product**.

- At the June 14, 2006 meeting, FDA recommended that GSK add an expectation of benefit statement to the labeling that informs consumers how much weight loss was seen on average in clinical trials. FDA requested that GSK send the supportive efficacy information for their labeling. Therefore, under **When using this product**, GSK added 2 bulleted statements which became bulleted statements 6 and 7, to address weight loss. The bulleted statements read as follows:

- [redacted]
- [redacted]

FDA's Response: Combine the the sixth and seventh bulleted statements, which become the fifth bulleted statement under **When using this product**, to read "for every 5 pounds you lose from diet alone, orlistat can help you lose 2-3 pounds more. In studies, most people lost 5-10 pounds over 6 months."

9. Under ***Warnings***, under **Stop use and ask a doctor if**, GSK added the following bulleted statement: "severe or continuous abdominal pain occurs. This may be a sign of a serious medical condition." GSK was responding to FDA's request to describe the potential signs and/or symptoms of pancreatitis and is added as a precautionary measure.

FDA's Response: This change is acceptable.

10. Under ***Warnings***, put a period after the pregnancy/breastfeeding warning.

11. Under ***Warnings***, under the "overdose" warnings, delete the word [redacted]

Directions

12. In the April 6, 2006 approvable letter and/or at the June 14, 2006 meeting, FDA advised GSK to make the following revisions under ***Directions***:

- [redacted]

FDA's Response: Make the first bulleted statement in ***Directions*** read as follows: "read the enclosed materials for complete directions and other important information".

- FDA stated that the Drug Facts label should adequately convey that the foundation of any weight loss program is to first emphasize an appropriate diet and exercise before medication is considered.

  GSK added a bulleted statement in ***Directions***, which became the second bulleted statement to read: "diet and exercise are the starting points for any weight loss program. ——— try these first before adding orlistat."

FDA's Response: The second bulleted statements are acceptable with two exceptions. Revise the second sentence to read "Try these first before adding orlistat." Add a third sentence to read "Check with your doctor before starting any exercise program."

- In the April 6, 2006 approvable letter, FDA recommended that GSK provide information to consumers that will allow them to calculate their body mass index (BMI) and understand what that value means. The proposed label did not convey information that will help a consumer at the point of purchase determine whether they are overweight or provide information as to when to consider initiating drug therapy. GSK added a bulleted statement in ***Other information***, (the fourth bulleted statement) to read as follows:

  - to determine if orlistat capsules are right for you, find your height on the chart to the right. If your weight is equal to or greater than the weight shown for your height, you can get the most benefit from weight loss using orlistat capsules.

FDA' Response: After reconsideration, we think the BMI chart belongs in the ***Directions*** section of **Drug Facts** rather than in ***Other information***. Therefore, we recommend that GSK move the BMI chart to ***Directions*** and make the third bulleted statement in ***Directions*** read as follows: [bullet] to see if orlistat capsules are right for you, find your height on the chart to the right. You should only start a weight loss program with orlistat if your weight is the same or more than the weight shown for your height."

- FDA stated to GSK that limiting the dose to 60 mg three times a day is appropriate for introduction of orlistat into the over-the-counter market. Therefore, GSK revised the directions (their bullets 3 and 4) to read as follows:
  - take 1 capsule with each meal containing fat
  - do not exceed 3 capsules daily

FDA's Response: These changes are acceptable with the following execptions: GSK should precede these two bullets with a bolded bulleted statement which reads: "for **overweight adults 18 years and older:**". This will become the fourth bulleted statement under ***Directions***. Then, the old bullets three and four (above) can follow as sub-bullets. The second sub-bullet,"do not exceed 3 capsules daily", should be revised to read "do not take more than 3 capsules daily".

- The fifth bulleted statement should tell consumers to use orlistat daily with a low-fat, reduced-calorie diet.

FDA also asked that GSK add a statement indicating that maximal weight loss effects are generally seen in the first six months.

GSK revised the fifth bulleted statement to read "continue daily use along with a reduced calorie, low-fat diet until you reach your weight loss goal. Most weight loss usually occurs within the first six months."

FDA's Response: Revise this bulleted statement again to read: "use along with a reduced-calorie, low-fat diet until you reach your weight loss goal. Most weight loss occurs in the first 6 months."

- FDA stated that the label should inform consumers that they may start to regain weight after stopping orlistat and that to maintain weight loss they may need to continue using orlistat capsules along with a low-fat, reduced-calorie diet.

Therefore, GSK added two bulleted statements (6 and 7) to read as follows:

- if you stop using orlistat, continue with a diet and exercise program
- you may start to regain weight after you stop taking orlistat. In order to maintain your weight loss, you may need to ——— taking orlistat along with a reduced calorie, low-fat diet.

FDA's Response: The sixth bulleted statement is acceptable. Revise the seventh to read: "if you start to regain weight after you stop taking orlistat, you may need to ——— taking orlistat along with your diet and exercise program.

- GSK repeated the need to take a multivitamin once daily, at bedtime, as the 8th bulleted statement. The statement is bolded. GSK intends this to be a reminder statement, and, as such, follows the series of orlistat use instructions.

FDA's Response: Revise this sixth bulleted statement to read as follows: "**take a multivitamin once a day, at bedtime, when using orlistat**".

Other Information

13.

- [redacted]

FDA Response: It is really not necessary to repeat this message again. It is stated in ***Directions***.

14. In the April 6, 2006 approvable letter, FDA recommended that GSK provide information to consumers that will allow them to calculate their body mass index (BMI) and understand what that value means. The proposed label did not convey information that will help a consumer at the point of purchase determine whether they are overweight or provide information as to when to consider initiating drug therapy.

[redacted]

FDA's Response: Incorporate the BMI chart and the bulleted statement about the BMI chart into ***Directions*** (see #11 above). Also, ***Other information*** should now consist of just two bullets as follows:

- store at 20-25°C (68-77°F)
- protect drug from excessive light, humidity and temperatures over 30°C (86°F)

Questions or comments?

15. In ***Questions or comments?***, FDA advised GSK to omit the Spanish statement. GSK made this change.

FDA's Response: This change is acceptable.

General format

16. At the June 14, 2006 meeting, FDA recommended that Drug Facts may be easier to read if the font is black. GSK agreed to print the final label with black text.

FDA's Response: This change is acceptable.

17. Revise bullet size to 5-point type size to be in accordance with 21 CFR 201.66 (d)(4).

C. Back Panel/Right

- Previously, FDA asked GSK to revise the last sentence in the tamper-evident statement to read "DO NOT USE THIS PRODUCT IF ANY OF THESE TAMPER-EVIDENT FEATURES ARE MISSING, TORN, OR BROKEN." GSK made this change.

FDA's Response: The Tamper-Evident feature is acceptable.

II. Refill Pack

A. Primary Display Panel (PDP)(120 mg)

- The changes recommended for the starter pack are applicable to the refill pack. Sponsor should make the appropriate changes to the PDP for the refill pack.

B. Drug Facts (Back Panel)

- The changes recommended for the starter pack are applicable to the refill pack. Sponsor should make the appropriate changes to the refill pack.

C. Side Panel

- GSK relocated the listing of package contents to the side panel. The starter pack has the listing of package contents on the top panel.

FDA's Response: This change is acceptable.

III. Bottle (60, 90, 120 ct)

General Label

GSK revised the bottle label so that the contents, particularly the warnings and directions, are consistent with Drug Facts labeling.

17. GSK now has to make further revisions to keep the bottle label consistent with the Drug Facts label (as discussed above in section II).

18. Revise the statement under the Drug Facts box which begins '[redacted] to "To get information in Spanish, ...". This suggestion was made because it is assumed that consumers who want more information in Spanish won't understand the statement - but may recognize the word "information".

IV. Read Me First (Keys to successful weight loss)

In the April 6, 2006 approvable letter, FDA stated that it was important to provide educational materials with the OTC product in lieu of the consultation that otherwise may be provided by a health care provider in the prescription setting. The educational materials included with GSK's first application were not tested for consumer understanding. Therefore, GSK should conduct testing that demonstrates consumer understanding of the materials. GSK discussed with FDA at the June 14, 2006 meeting whether the "Read Me First" guide could be included as labeling, that does not replace the existing in-pack literature, if the guide was tested in a label comprehension study. FDA agreed.

FDA recommends that GSK make the following changes to the leaflet, "Read Me First, Keys to successful weight loss":

- Delete all page references to the Companion Guide and/or the Healthy Eating Guide. These are not considered part of FDA's approved labeling for orlistat.
- Under "Use Alli as directed", insert the words "Drug Facts" before the word "label".
- Under "Expect steady, gradual weight loss", revise the first sentence to read "Set realistic goals that result in steady gradual weight loss".
- Under "Expect steady, gradual weight loss", revise the expectation of benefit statement to read: [redacted]
- Under "Expect steady, gradual weight loss", replace the words [redacted] in the second paragraph with "reduced-calorie, low-fat diet".
- Under "Eat right", delete the paragraph which begins "Choose foods low in fat." but keep the subtitle. Make it part of the subtitle of the next paragraph (i.e., "Choose foods low in fat; reduce calories and portion sizes. While choosing low-fat foods.....").

- Under "Write it down", revise the first sentence to read "It is important for your weight loss success to record what you eat and drink. "
- Under "Stick to your program", delete ——— from the third sentence which reads "Don't expec ——— to follow your program....".

V. Supporting Materials

Although the rest of the supporting materials were not tested for label comprehension and are not considered labeling, FDA has the following comments about some of the supporting materials:

Reviewer's Recommendations

The following comments can be conveyed to the sponsor:

I. Starter Pack (60, 90, 120ct) and Refill Pack (120ct)

A. Principal Display Panel (PDP) (60, 90, 120ct)/Top Panel

1. Delete the promotional statemen

B. Back Panel (Drug Facts)

2. Under *Use*, delete the period at the end of the bulleted statement "for weight loss in overweight adults, 18 years and older, when used along with a reduced calorie and low fat diet".

3. Under *Use*, revise "reduced calorie and low fat diet" to read "reduced-calorie and low-fat diet". Note the use of the hyphens in "reduced-calorie" and "low-fat".

4. Under ***Warnings***, under **Allergy alert**, add a colon after the word "alert".

5. Under ***Warnings***, under "**Do not use**", bold the first bulleted statement "if you are taking cyclosporine".

6. Under ***Warnings***, under "**Ask a doctor or pharmacist before use if you are**", combine the first and second bulleted statements to read: "**taking warfarin (blood thinning medicine)**, or taking medicine for diabetes or thyroid disease. Your medication dose may need to be adjusted."

7. Under Warnings under "**When using this product**", revise the first sentence in the first bulleted statement to read "**take a multivitamin once a day, at bedtime.**"

8. Under ***Warnings*** under "**When using this product**", revise the second bulleted statement to read "follow a well-balanced, reduced-calorie, low-fat diet. Try starting this diet before taking orlistat. See enclosed materials for tips on how to follow a well-balanced, reduced-calorie, low-fat diet."

9. Under ***Warnings*** under "**When using this product**", combine the proposed third and fourth bulleted statements into one bulleted statement (which becomes the third bulleted statement under **When using this product**) to read: "orlistat works by preventing the absorption of some of the fat you eat. The fat passes out of your body, so you may have bowel changes. You may get : [bullet] gas with oily spotting [bullet] loose stools [bullet] more frequent stools that may be hard to control".

10. Under ***Warnings*** under "**When using this product**", shorten the proposed fifth bulleted statement [ ] to "eating a low-fat diet lowers the chance of having these bowel changes". This becomes the fourth bulleted statement under **When using this product**.

11. Under ***Warnings*** under "**When using this product**", combine the proposed sixth and seventh bulleted statements, which becomes the fifth bulleted statement under "**When using this product**", to read "for every 5 pounds you lose from diet alone, orlistat can help you lose 2-3 pounds more. In studies, most people lost 5-10 pounds over 6 months."

12. Under ***Warnings***, put a period after the pregnancy/breastfeeding warning.

13. Under ***Warnings***, under the "overdose" warnings, delete the word [ ]

14. Under ***Directions***, take the last bulleted statement which reads [ ] Revise the

'. The proposed first bulleted statement, "for overweight adults 18 years and older", will become the fourth bulleted statement under ***Directions*** (see #16 below).

15. Under ***Directions***, revise the second bulleted statement about diet and exercise to read: "diet and exercise are the starting points for any weight loss program. Try these first before adding orlistat. Then, add a third sentence to read: "Check with your doctor before starting any exercise program."

16. Because we think the BMI chart belongs in the ***Directions*** section of **Drug Facts** rather than in ***Other information***, move the BMI chart to ***Directions*** and make the third bulleted statement under ***Directions*** read as follows: "[bullet] to see if orlistat capsules are right for you, find your height on the chart to the right. You should only start a weight loss program with orlistat if your weight is the same or more than the weight shown for your height."

17. Under ***Directions***, bold the fourth bolded bulleted statement to read as follows: "**for overweight adults 18 years and older:**" Then, your current bullets 3 and 4 can follow as sub-bullets under bullet 4. Also, revise the second sub-bullet to read "do not take more than 3 capsules daily." The entire three bullets read as follows:
    - **for overweight adults 18 years and older:**
      - take 1 capsule with each meal containing fat
      - do not take more than 3 capsules daily

18. Revise the fifth bulleted statement under ***Directions*** to read: "use along with a reduced-calorie, low-fat diet until you reach your weight loss goal. Most weight loss occurs in the first 6 months."

19. Revise the seventh bulleted statement under ***Directions*** to read: "if you start to regain weight after you stop taking orlistat, you may need to taking orlistat along with your diet and exercise program".

20. Revise the multivitamin statement under ***Directions*** (the eighth bulleted statement) to read "**take a multivitamin once a day, at bedtime, when using orlistat**".

21. Under ***Other information***, because FDA believes that the BMI chart and instructions on how to use the BMI chart should be moved to ***Directions***, and since the third bulleted statement about diet and exercise is redundant and can be deleted, the only two bullets remaining in ***Other information*** will be the storage information (bulleted statements 1 and 2). In addition, revise bullet #2 to read: "protect drug from excessive light, humidity and temperatures over 30°C (86°F).

22. Revise bullet size (for all bulleted statements in Drug Facts) to 5-point type size to be in accordance with 21 CFR 201.66 (d)(4).

23. Under the Drug Fact box, we recommend revising the statement which begins [redacted] to "To get information in Spanish.....". We think that having the word "information" in the sentence might be useful to Spanish consumers who might not understand English well but might recognize the word "information".

We have included a mockup of the revisions that FDA is requesting for **Drug Facts** which can be found in Table1 (at the end of this review). Please remember that this mockup is for content purposes only. The font sizes for title, headings, subheadings, condensed text, bullets and other graphic features must be in accordance with 21 CFR 201.66.

II. Bottle (60, 90, 120ct)

23. Revise bottle label to be consistent with the changes being made to the Drug Facts labels of the starter and refill packs. We have included a mockup of a bottle label with the suggested revisions for your convenience. This is located at the end of this review in Table 2.

III. Read Me First (Keys to successful weight loss)

24. Delete all page references to the Companion Guide and/or the Healthy Eating Guide. These are not considered part of FDA's approved labeling for orlistat.

25. Under "Use Alli as directed", insert the words "Drug Facts" before the word "label".

26. Under "Expect steady, gradual weight loss":

    a. Revise the first sentence to read "Set realistic goals that result in steady gradual weight loss".

    b. Revise the expectation of benefit statement to read: [redacted]

    c. Replace the words [redacted] in the second paragraph with "reduced-calorie, low-fat diet."

27. Under "Eat right", delete the paragraph which begins "Choose foods low in fat." but keep the subtitle. Make it part of the subtitle of the next paragraph (i.e., "**Choose foods low in fat; reduce calories and portion sizes**. While choosing low-fat foods.....").

28. Under "Write it down", revise the first sentence to read "It is important for your weight loss success to record what you eat and drink."

29. Under "Stick to your program", delete [redacted] from the third sentence which reads "Don't expec[redacted] to follow your program....".

IV. Supporting Materials

Although the rest of the supporting materials were not tested for label comprehension and are not considered labeling, FDA has the following comments about some of the supporting materials:

[redacted]

1/9/07

Arlene Solbeck, MS
Senior Regulatory Review Scientist
Division of Nonprescription Regulation Development

1/9/07

Helen Cothran, BS
Team Leader
Division of Nonprescription Regulation Development

3 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4

NDA 21-877
HFD-510: Parksl/Colman/Golden/Mele/Sahlroot/Rosebraugh
ONP: Division File
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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:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alli (orlistat) Capsules, 60 mg

We also refer to the meeting between representatives of your firm and the FDA on June 14, 2006. The purpose of the meeting was to discuss deficiencies identified in the Agency's approvable letter issued on April 6, 2006.

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) 827-6416.

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

Enclosure: Meeting minutes

MEETING MINUTES

MEETING DATE: June 14, 2006

TIME: 11:00 AM –12:00 Noon

LOCATION: White Oak Campus, Building 22

APPLICATION: NDA 21-887 Alli (orlistat) Capsules

TYPE OF MEETING: Type B; End of Review

MEETING CHAIR: Eric Colman, M.D.; Acting Deputy Director, DMEP

MEETING RECORDER: Patricia Madara

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

CDER Participants:

Office of Drug Evaluation II

Curtis Rosebraugh, M.D., MPH	Deputy Director

Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D.	Acting Director
Eric Colman, M.D.	Acting Deputy Director
Julie Golden, M.D.	Medical Officer
Pat Madara, M.S.	Regulatory Project Manager

Office of Nonprescription Products

Charles Ganley, M.D.	Director

Division of Nonprescription Clinical Evaluation

Andrea Leonard-Segal, M.D.	Director
Karen Feibus, M.D.	Acting Clinical Team Leader
Linda Hu, M.D.	Medical Officer
Susanna Weiss, Ph.D., J.D.	Social Science Analyst
Keith Olin, R.Ph.	Regulatory Project Manager
Leah Christl, Ph.D.	Supervisory Project Manager

Division of Nonprescription Regulation Development

Helen Cothran, B.S.	Interdisciplinary Scientist Team Leader
Arlene Solbeck, M.S.	Senior Regulatory Review Scientist

Office of Drug Safety, Division of Drug Risk Evaluation

Joslyn Swann, Pharm.D.	Safety Evaluator
Lanh Green, Pharm.D., M.P.H.	Safety Evaluator Team Leader
Cynthia Kornegay, Ph.D.	Epidemiology Reviewer

Office of Regulatory Policy

Janice Weiner, J.D., M.P.H.	Regulatory Counsel

EXTERNAL ATTENDEES

GlaxoSmithKline Participants:

David Schifkovitz	Director, Regulatory Affairs
George Quesnelle	President, Consumer Healthcare North America
John Dent	GSK Consultant (retired Sr. Vice President, Research and Development, GSK)
Steve Burton	Vice President, Weight Control Business Unit
Randy Koslo	Director, Medical Affairs
Vidhu Bansal	Director, Medical Affairs
Cecilia Hale	Senior Statistician, Biostatistics and Data Management
Andrea Harkins	Senior Consumer Research Manager
Erin Oliver	Associate Director, Regulatory Affairs
Susan Schwartz	Director, New Product Research
Dan Keravich	Associate Director, Regulatory Policy

Background and Summary:

On June 6, 2005, GSK submitted an NDA (21-887) for Alli (orlistat), 60 mg Capsules, seeking approval for over-the-counter use. The FDA issued an approvable (AE) letter on April 6, 2006. On April 13, 2006 the firm submitted an official request for an end-of-review meeting with the Agency. A briefing document dated May 17, 2006, containing a specific list of questions for discussion was also received. Draft answers to the questions were sent to the firm on June 9, 2006. Based on the draft information, GSK made further revisions to the Alli labeling. These new changes and other issues were discussed at the June 14, 2006 meeting.

In addition, on June 14, 2006, a separate meeting was held with the Division of Nonprescription Clinical Evaluation and GSK to discuss specific issues related to the design of the proposed label comprehension and self-selection study protocols. Information from that meeting is not included here.

Bullet format. Note: <u>GSK comments made during the meeting are in italics and Agency responses made during the meeting are in bold font. The draft answers sent to the sponsor on June 9, 2006 are in normal font.</u>

1. Does the Agency agree with GSK's proposed label revisions to the Drugs Facts and carton back panel to address label observations noted in the April 6, 2006 Action Letter?

<u>Agency Response:</u>

- In the *Use* section, your statements about diet and exercise should send a clear message that diet and exercise should be tried before using orlistat, that orlistat should be used in addition to diet and exercise for weight loss and that orlistat should not be substituted for diet and exercise. However, to simplify the Use section, you could consider placing these statements in other sections of the label, e.g. *Directions* or When using this product. You may want to test several labels.

- We recommend revising the heading and content of the Cyclosporine/Organ transplant alert. The heading should be Organ transplant/Cyclosporine alert, and the content may need to be expanded to include the names of other immunosuppressants if data suggest that co-administration with orlistat may reduce their absorption. The warning should inform consumers who use cyclosporine (and perhaps other immunosuppressants) that orlistat can lower blood levels which could lead to organ transplant rejection. We are not certain if yellow highlighting enhances comprehension of the highlighted text or whether highlighting positively or negatively affects comprehension of the remainder of the label. You may want to evaluate this in your label comprehension studies.

<u>Additional GSK comment:</u>

The sponsor noted that they had changed the label to exclude anyone who has had an organ transplant, indicating that they wanted to eliminate this population from using orlistat.

<u>Additional Agency comment:</u>

The Agency asked which drugs were currently being used by transplant patients and asked for what other diseases cyclosporine might be used. FDA stated that warnings not to use orlistat should cover three populations (related to transplants / cyclosporine use):

- **Transplant recipients**
- **Transplant recipients taking cyclosporine**
- **Patients taking cyclosporine for other reasons, including psoriasis and arthritis**

Thus, in addition to the Organ transplant/Cyclosporine alert, a warning similar to "Do not use if you are taking cyclosporine" should be on the label to address populations who are taking cyclosporine for indications other than prevention of a transplant rejection.

Additional GSK comment:

The sponsor pointed out that the medical community was "moving away" from prescribing cyclosporine to transplant recipients; however, some patients are still using the drug. They also pointed out that, while cyclosporine is used for psoriasis and arthritis, the biggest danger occurred when it was being used as an immunosuppressant, as it was for transplant recipients.

- In the *Warnings* section,

  In the *Ask a doctor before use if you have* section, your version of the gall bladder problems, kidney stone and pancreatitis warning seems to suggest that consumers should only be concerned if they have these diagnoses now. You should also provide a message that people with a history of gallbladder problems, kidney stones, and pancreatitis should ask a doctor before use.

Additional GSK comment:

GSK noted that they had revised the statement to read "Ask a doctor before use if you have ever had..."

Additional Agency comment: This change was acceptable.

- In When using this product:

  In the list of side effects, that bowel movements may be difficult to control.

  - Add a bullet explaining that orlistat can reduce the absorption of some vitamins from the intestines.

Additional GSK comment:

The sponsor added a statement explaining that orlistat can reduce vitamin absorption and deleted the statement about

Replace the last bullet with an expectation of benefit statement that informs consumers how much weight loss was seen on average in clinical trials. You may refer to the text and chart on page 3 of the *Companion Guide* for an example; however, the information conveyed needs to be modified for Drug Facts and other labeling as follows:

- The statement should explain the period of time over which the weight loss was seen (e.g., 6 months or 1 year).

- The data presented should be in line with the average weight loss seen in clinical trials.

- You should indicate that individual results vary.

Additional Agency comment:

FDA acknowledged that GSK made these requested changes in the draft label. FDA asked GSK to submit a summary of the clinical data supporting their efficacy claims and to include a statement noting that most weight loss occurs within the first six months of use.

Additional GSK comment:
GSK agreed to provide supporting data for their efficacy claims and to add language indicating most weight loss occurs within the first six months.

- We recommend that you change the Stop use and ask a doctor warning to read as follows:

  Stop use and ask a doctor if
  •severe or continuous abdominal pain occurs. This may be a sign of a serious medical condition.

Additional GSK comment: *This statement has been added.*

- In the *Directions* section:
  - The fifth bulleted statement should tell consumers to use orlistat daily with a low fat, reduced calorie diet.
  - The sixth bulleted statement should inform consumers that they may start to regain weight after stopping orlistat and that to maintain weight loss they may need to continue using orlistat capsules along with a low fat, reduced calorie diet.

Additional GSK comment:

GSK agreed to these changes.

Additional GSK comment:

GSK noted that this section was revised accordingly.

Additional GSK comment:

The sponsor noted that this section had been eliminated to provide space for other label changes.

- Drug Facts may be easier to read if the font is black. It is unclear from the copy of the draft labeling if the font is black or grey.

Additional GSK comment:

GSK apologized for the grey font and indicated that it should be black.

2. Does the Agency agree with GSK's proposal for the addition of the "Read Me First - Keys to Successful Weight Loss" as a means of communicating essential elements in behavioral modification associated with dieting and Orlistat use for weight loss as noted in Item #9 of the April 6, 2006 Action Letter?

   Agency Response:

   - Yes, we agree with your proposed addition. However, we are unclear as to whether *Read Me First: Keys to Successful Weight Loss* replaces any of the behavioral program materials included in the NDA submission.

   - A statement is needed that before starting an exercise regimen consumers should discuss the exercise program with a doctor (both in the label and *Read Me First—Keys to Successful Weight Loss* insert).

Additional GSK comment:

GSK indicated that "Read Me First: Keys to Successful Weight Loss" was an additional guide and did not replace anything previously submitted. They also included statements in the Drug Facts panel and in the "Read me first" label recommending that people discuss an exercise program with their doctor before starting.

- *Read Me First—Keys to Successful Weight Loss* will be part of Alli labeling. Additional specific label comments follow at the end of answers to questions.

- The information contained in *Read Me First—Keys to Successful Weight Loss* should be consistent with Drug Facts labeling (e.g. the expectation of benefit statement).

Additional GSK comment:

GSK noted that the panel information was now identical to the Drug Facts labeling.

- If *Read Me First—Keys to Successful Weight Loss* encapsulates and summarizes the behavioral messages contained in the Alli Companion Guide, then you should test consumer comprehension of this insert. Ensure that all messages in this insert are data driven. Add a qualifier to let people know that they need to eat in moderation and still count calories.

Additional GSK comment:

The sponsor noted that consumer understanding will be tested in a label comprehension study.

- Choose pictorial images for *Read Me First—Keys to Successful Weight Loss* and your other behavioral support materials that reinforce the healthy eating choices promoted by the Alli program

Additional GSK comment:

GSK noted that the picture had been revised to show healthier foods.

3. Does the agency agree with the protocol design and associated questionnaire to be used in Label Comprehension testing?

   Agency Response:

   A. There is a need for additional questions that more accurately and comprehensively test distinct pieces of information in the label. We would like to be reassured that consumers have assimilated each of the label concepts listed below. Ideally, each question should address one concept (one cognitive step) at a time.

      - Product Use and Target Population
        - That the medication is only one part of a complete weight loss program.
        - The age restriction for product use (i.e., it is for adults/18 years and older).
        - The ability to read the *height and weight* chart.

      - Multivitamin Use
        - When using orlistat, do you need to take anything else?
        - How often do you need to take the multivitamin?
        - When should you take the multivitamin?

      - Side Effects
        - Do consumers understand that orlistat use may cause unpleasant changes in bowel habits if they do not reduce the amount of fat in their diets?

      - Duration of Use
        - When should a consumer stop taking orlistat?
        - When a consumer decides to stop using orlistat, is there anything else he/she should do?
        - What should a consumer do if he/she stops using orlistat and begins to regain lost weight?

   B. We have some reservations and questions regarding the answer choices that might be coded as *correct* or *acceptable*. For each question, describe exactly which responses in the interviewer's sheets will be coded as *correct* and which will be coded as *acceptable* so that we can determine if we agree with you.

   C. We do not agree with the question format and content proposed for testing comprehension of the new package insert *Read Me First: Keys to Successful Weight Loss*. The use of scenarios as proposed in your draft study will bias the study results because:
      - Too much information is disclosed

- Some scenarios are too general and simplistic
- The "FOLLOW"/ "NOT FOLLOW" answers are too limited (50/50 chance of answering correctly)

Rewrite your scenarios to avoid biasing the study results. You may also consider introducing some simple questions with open-ended responses.

4. *Does the agency agree with the protocol design and associated questionnaire to be used in cyclosporine self-selection testing?*

Agency Response:

- The following statement in the flyer used for recruitment can bias results of the self-selection study and should be deleted: *It is important that the information on the label is correctly understood by the consumer so they can decide for themselves whether the product is appropriate to use.* This statement cues subjects to more closely examine the label for the proper self-selection criteria.

- The self selection question should read: *Is this product appropriate for you to use.* The phrase, *Based on what you read,* prompts the participant to re-examine the label more closely and does not simulate an actual self-selection situation.

- On page 25 of the self-selection protocol, it is appropriate to ask subjects to read the label and to tell them that they will be able to refer to the label during the survey. However, prompting participants to read the *entire* label, to refer to the label *as often as they would like*, and to *not guess at the answers but instead refer to the label*, does not simulate a "real-life" situation and may bias your results.

- The confidentiality disclosure and study participation agreement form should be free of bias.

- On page 66 of your submission (page 28 of the self-selection protocol), question 11 should be asked before question 10 to avoid biasing subject response.

- Submit information you may have on concomitant use of orlistat and other immunosuppressant drugs. Does orlistat reduce the absorption of other lipid-soluble immunosuppressant drugs such as tacrolimus?

5. Does the Agency agree with GSK's proposal for an interim safety update to address the Citizen's Petition on Orlistat?

Agency Response:

Any information you provide to address the citizen petition should be submitted to the appropriate docket. We remind you that information submitted to the docket will be in the public domain. If you choose to also submit the same information as part of your safety update, that would be acceptable. All interim safety data should be submitted as a Safety Update to the NDA.

Additional (pre-meeting) Agency Comments:

Label Comments for *Read Me First—Keys to Successful Weight Loss*

Section: Expect steady, gradual weight loss

It is not clear what *manage your weight loss expectations* means. Does it mean that consumers should choose realistic or reasonable weight loss expectations?

may be able to adapt the information from page 3 of the Companion Guide that states: *for every five pounds you lose through diet, the Alli capsules will take off two to three more.*

Additional GSK comment:

GSK commented that the statement was changed and clarified using language from the Companion Guide as recommended by FDA

- Change the third sentence to include information to convey that the amount of weight lost will depend on the starting weight and on how closely the consumer follows the recommended diet and the Alli program. Also convey that people who are more overweight usually lose more weight than those who are less overweight.

Additional GSK comment:

The sponsor agreed to this revision.

Section: Change your behavior

- In *Focus on behaviors that affect your weight,* . These behaviors affect weight outside the Alli program as well.

Additional GSK comment:

The sponsor agreed to this revision.

Section: Eat right

- In *Eat a balanced diet*, add the word *healthy* to the statement as follows:
  one that includes a variety of healthy foods.

- *One easy way to be sure you're eating the right food in the right portions is to plan your menus.*

Additional GSK comment:

The sponsor agreed to all Agency recommendations for the "Eat Right" section.

Section: Write it down

- Move this section up so that it follows the Eat Right section. This section logically follows the discussion about choosing the right kinds and amounts of foods.

Additional GSK comment:

This section has been moved.

Section: Develop a routine

- In *Consistency is important to your success*, the paragraph should convey for consistency with dose and clarity that

  consumers should make taking the capsule part of the meal routine, so they will notice something is missing if they do not take a capsule.

Section: Get active

- Add a statement that consumers should speak with a doctor before starting a new exercise plan.

- To improve clarity, put the *You don't need to do it all at once* paragraph before the *Start small and work your way up* paragraph.

Additional GSK comment:

A statement has been added telling consumers to speak with a doctor before starting an exercise program. The "You don't need to do it all at once" paragraph has been placed before the "Start small and work your way up" paragraph.

Use consumer-friendly language to convey your messages throughout *Read Me First—Keys to Successful Weight Loss*

Additional Agency comments:

Post-meeting note: FDA verified that the regulations at 21 CFR 201.15(c)(1) require that the label be in English.

Minutes Preparer: _____*/s/*_____
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Chair Concurrence: _____*/s/*_____
Eric Colman, M.D.
Acting Deputy Director
Division of Metabolism and Endocrinology 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
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