CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-362

OTHER REVIEW(S)

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	April 28, 2009
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrinology Products
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, Pharm D, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Welchol (Colesevelam Hydrochloride for Oral Suspension) 1.875 g and 3.75 g
Application Type/Number:	NDA# 22-362
Applicant:	Daiichi Sankyo Pharma
OSE RCM #:	2008-1647

CONTENTS

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Metabolism and Endocrinology Products to evaluate the product for its potential to contribute to medication errors. Pouch labels, carton labeling and insert labeling were evaluated to identify areas that could lead to medication errors.

1.2 REGULATORY HISTORY

This Application is a 505(b)(2) which provides for a new dosage form ((b) (4) for Oral Suspension) for Welchol. The reference listed drug (RLD) for this product is Welchol Tablets (NDA 21-176) which was approved on May 26, 2000. The Applicant is proposing a single Welchol package insert based on the currently approved tablet labeling with appropriate sections modified to incorporate the (b) (4) for oral suspension dosage form.

1.3 PRODUCT INFORMATION

Welchol is a bile acid sequestrant indicated as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol in patients with primary hyperlipidemia as monotherapy or in combination with an hydroxymethyl-glutaryl-coenzyme A reductase inhibitor. Additionally, Welchol is indicated to improve glycemic control in adults with type 2 diabetes mellitus.

Welchol is currently available as a 625 mg tablet with the recommended dose of 6 tablets once daily or 3 tablets twice daily. The proposed Welchol product will be available as a (b) (4) for oral suspension in single-dose packets in strengths of 1.875 gram and 3.75 gram. The recommended dose is one 3.75 gram packet once daily or one 1.875 gram packet twice daily. To prepare the oral suspension, the entire contents of one packet must be emptied into a glass or cup. Then 4 to 8 ounces of water should be added and the mixture should be stirred well and drank. The 1.875 gram packet will be supplied in cartons of 60 count and the 3.75 gram packet will be supplied in cartons of 30 count.

2 METHODS AND MATERIALS

2.1 FDA'S ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

Since Welchol is a currently marketed product, the FDA Adverse Event Reporting System (AERS) was searched for post-marketing safety reports related to Welchol on December 11, 2008. The MedDRA High Level Group Term "Medication Error" and Preferred Term "Pharmaceutical Product Complaint" along with the active ingredient (colesevelam hydrochloride), proprietary name (Welchol), and verbatim terms "Welc%" and "Colese%" were used to perform the search.

The cases were manually reviewed to determine if a medication error occurred. Those cases that did not describe a medication error with Welchol were excluded from further analysis. If an error occurred, the staff reviewed the case to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. The cases that described a medication error possibly relevant to this review of this product were categorized by type of

error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

2.2 LABELS AND LABELING RISK ASSESSMENT

This section describes the methods and materials used by DMEPA staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because our staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The DMEPA staff uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted to the Electronic Document Room (EDR) on August 15, 2008 the following labels and labeling for DMEPA to review (see Appendices A through J for images):

- Pouch Label: 1.875 g (Child-resistant and (b) (4)
- Pouch Label: 3.75 g (Child-resistant and (b) (4)
- Carton Labeling (60 count): 1.875 g (Child-resistant and (b) (4)
- Carton Labeling (30 count): 3.75 g (Child-resistant and (b) (4)
- Professional Sample Pouch Label: 1.875 g (Child-resistant and (b) (4)
- Professional Sample Pouch Label: 3.75 g (Child-resistant and (b) (4)

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- Professional Sample Carton Labeling (14 count): 1.875 g (Child-resistant and (b) (4) (b) (4)
- Professional Sample Carton Labeling (7 count): 3.75 g (Child-resistant and (b) (4) (b) (4)
- Insert Labeling (no image)

3 RESULTS

3.1 AERS DATABASE SEARCH

Our search yielded a total 11 pertinent cases that were classified by the following types: wrong patient (1), wrong drug (1), and product complaints (9).

3.1.1 Wrong Patient

The case involving the wrong patient occurred when a Welchol prescription was dispensed with the name of the patient's spouse. The patient's spouse discovered the error and had the pharmacy correct the prescription.

3.1.2 Wrong Drug

This case involved a patient receiving Welchol 625 mg instead of Renagel 800 mg, which resulted in the patient experiencing "nausea and sickness". The error was discovered by the patient's physician. The reporter states the error was caused by "high stress day" and being "short staffed". The patient recovered. Because this wrong drug case appears to be an isolated incident, it does not have an impact on this proposed product.

3.1.3 Product Complaints

There were nine cases of complaints involving Welchol. The first case reported orthographic similarity of the names Welchol 625 mg and Carvedilol 6.25 mg when they are scripted. In the remaining eight cases patients complained that the Welchol tablets are large and difficult to swallow. Two patients reported experiencing gagging due to the difficulty in swallowing the tablets. Another patient reported a Welchol tablet became lodged in his "voice box", which resulted in an ER visit. The patient stated no treatment was needed in the ER as the tablet dissolved. The remaining patients who complained about the large size of the tablet and it being hard to swallow, did not report any adverse outcomes.

This new proposed dosage form (powder for oral suspension) will provide an alternative for patients having difficultly swallowing the currently marketed Welchol tablets.

3.2 LABELS AND LABELING RISK ASSESSMENT

Our labels and labeling review noted several areas of needed improvement.

3.2.1 All Labels and Labeling

The Applicant plans to market a child-resistant and a (b) (4) packaging configuration.

The established name does not appear to be at least one-half the size of the proprietary name.

The same gold, green and blue colors are used on all labels and labeling.

The product strengths do not appear prominent and do not follow the proprietary name, established name, and dosage form.

The preparation instructions state the amount of water required in ounces only.

The "dash symbol" (-) is used to represent the range of the amount of water required (4-8 ounces).

The dosage form descriptor (b) (4) appears above the proprietary name, Welchol.

3.2.2 Carton Labeling (Trade and Professional Sample)

The net quantity appears immediately below the established name and dosage form.

The strength does not appear in conjunction with the proprietary name and established name on the side panel.

4 DISCUSSION

Our label and labeling review noted several areas of needed improvement.

4.1 PACKAGING CONFIGURATION

The Applicant is proposing to market a child-resistant and a (b) (4) packaging configuration for this product. (b) (4)

(b) (4)

4.2 OVERLAPPING COLOR SCHEMES

The Applicant uses the same colors (i.e. gold, blue and green) to differentiate the strengths and also to represent whether the product is child resistant or (b) (4) Moreover, the 'sugar free' statements are presented in green or gold on all labels and labeling. Therefore, the labels and labeling appear similar. Using these overlapping colors on all the labels and labeling contributes to their similarity and diminishes the usefulness of color for product strength differentiation. Based on postmarketing experience, labels and labeling that are not adequately differentiated increase the risk of confusion and also contribute to product selection errors that can lead to an over or under dose because the wrong strength is dispensed and administered. Additionally, although it is important to distinguish child-resistant (b) (4) labels and labeling, we do not feel these colors should be the same colors that are used to differentiate the product strengths.

4.3 PRESENTATION OF THE ESTABLISHED NAME

Due to the light weight font used, the established name does not appear to be at least one-half the size of the proprietary name which is not in accordance to 21 CFR 201.10(g)(2) which states: "the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features."

4.4 PRESENTATION OF THE PRODUCT STRENGTH AND NET QUANTITY

The product strengths are located in the top right hand corner of the container label and carton labeling and the net quantity appears below the established name on the carton labeling. This is counter to the usual placement for strength and net quantity. The net quantity statement is typically placed in a location on the principle display panel that does not compete with the strength and the strength is presented immediately following the established name (e.g. proprietary name, established name, dosage form, and followed immediately by the product strength without any intervening matter). Practitioners are accustomed to this layout and when items appear in different locations it takes longer to locate and process the information. Additionally, the presentation of the product strengths lack prominence because of the small font size used.

4.5 PREPARATION INSTRUCTIONS

The preparation instructions state the amount of water to use in ounces. Patients may not be familiar with how to covert ounces into cups. Having this essential information presented in cups will also help to ensure patients add the correct amount of water and will therefore minimize the risk of the solution being too concentrated or too diluted. Additionally, the (b) (4)

4.6 PRESENCE OF DOSAGE FORM DESCRIPTOR

The descriptor (b) (4) appears above the trade name, Welchol. This descriptor is unnecessary and inconsistent with the USP definition of this type of pharmaceutical dosage form which is 'for Oral Suspension'.

4.7 LACK OF PRODUCT STRENGTH ON SIDE PANEL OF CARTON LABELING

The product strength does not appear with the proprietary name and established name on the side panel of the carton labeling. If the products are shelved with the side panels facing out, the risk of selection error would be increased. In order to minimize the risk of selection errors, each presentation of the proprietary and established name should be accompanied by the product strength, especially since this product is available in 2 different strengths.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate the overlapping colors used to represent the product strengths and child-resistant and non-child-resistant properties, in addition to the presentation of essential information introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention and Analysis would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Mildred Wright, OSE project manager, at 301-796-1027.

5.2 COMMENTS TO THE APPLICANT

A. All Labels and Labeling

1. We are aware that your Application for a (b) (4) exemption is pending. Thus, the comments below relating to the overlapping color schemes for both package configurations are contingent upon your exemption being granted. If your exemption is not granted prior to approval of this NDA supplement, then we understand you will withdraw the non-child-resistant packaging configuration.

   The labels and labeling for the two product strengths and packaging configurations (child-resistant vs. (b) (4) appear similar. (b) (4) The color blue is utilized to represent the 3.75 mg strength and the colors blue and green are utilized to represent the child-resistant labels and labeling for both strengths. Moreover, the 'sugar free' statements are presented in green or gold on all labels and labeling. Using the same gold, blue and green overlapping colors on all the labels and labeling contributes to their similarity and diminishes the usefulness of color for product strength differentiation. Revise the colors used to differentiate the child-resistant labels and labeling from the (b) (4) labels and labeling so that they do not overlap with any of the colors used to differentiate the strengths. Additionally, ensure that the colors chosen for product strength differentiation and representing whether or not the packaging is child resistant are utilized consistently throughout all labels and labeling.

2. Although the established name is presented as half the size of the established name, the light weight font used decreases the prominence of the established name. Increase the prominence of the established name and dosage form in accordance with 21 CFR 201.10(g)(2) which states that "the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into

account all pertinent factors, including typography, layout, contrast and other printing features."

3. Relocate the product strength so that it appears immediately following the established name and dosage form. This is the format that most healthcare practitioners are accustomed to. Additionally, increase the prominence of the product strength by increasing the font size of this information. For example:

Welchol

(Colesevelam HCl for Oral Suspension)

XXX g

4. For the preparation instructions, revise the statement [redacted] (b) (4) to read "Add 1/2 cup to 1 cup (4 to 8 ounces) of water." Patients may not be familiar with how to convert ounces into cups. Having this essential information presented in cups will also help to ensure patients add the correct amount of water while also providing adequate instructions to healthcare practitioners administering this product. Additionally, revise [redacted] (b) (4)

5. Delete the dosage form descriptor [redacted] (b) (4) above the proprietary name as this descriptor is unnecessary and inconsistent with the USP definition of this type of pharmaceutical dosage form which is 'for Oral Suspension'.

B. Carton Labeling (Trade and Professional Sample)

1. Include the product strengths on the side panel following the dosage form. If the products are shelved with the side panels facing out, the risk of selection error would be increased without the product strength statement. In order to minimize the risk of selection errors, each presentation of the proprietary and established name should be accompanied by the product strength.

2. Relocate the net quantity to appear in the top right hand corner or bottom right hand corner of the principle display panel. Its current location following the dosage form is typically the location used for the product strength. Relocating the net quantity will allow room for the product strength to be more prominent and will minimize competition between these statements.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

(J) 10 pages of OtherReview has been withheld in full immediately following this page as B4 CCI/TS

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

/s/

Deveonne Hamilton-Stokes
4/28/2009 04:36:11 PM
DRUG SAFETY OFFICE REVIEWER

Todd Bridges
4/28/2009 04:43:55 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/28/2009 05:37:46 PM
DRUG SAFETY OFFICE REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-362 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: Welchol (b) (4) for Oral Suspension
Established Name: colesevelam
Strengths: 1.875 grams, 3.75 grams

Applicant: Daiichi-Sankyo
Agent for Applicant (if applicable): N/A

Date of Application: 8/15/08
Date of Receipt: 8/15/08
Date clock started after UN: N/A
Date of Filing Meeting: 10/10/08
Filing Date: 10/14/08
Action Goal Date (optional): 5/15/09 User Fee Goal Date: 6/15/09

Indication(s) requested: As an adjunct to diet to:
1. Reduce elevated LDL-C in patients with primary hypercholesterolemia as monotherapy or in combination with a statin.
2. Improve glycemic control in adults with type 2 diabetes mellitus.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1. This application is a paper NDA YES ☐

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

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

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

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

   Additional comments:

3. This application is an eCTD NDA. YES x

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

Additional comments:

- Patent information submitted on form FDA 3542a? YES x NO ☐

- Exclusivity requested? YES, _____ Years NO x
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X[NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES x NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO x

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☐ NO X
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

NOTE:due to the insolubility of the drug, an in-vitro BE study was conducted.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO ☐

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

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: N/A

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO x
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 3/13/08 (under NDA 21-176) NO
  If yes, distribute minutes before filing meeting.

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

Project Management

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

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

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

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

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO x
  NOTE-this is only a new dosage form, so the tradename is already established.
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A x YES ☐ NO ☐

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

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

If Rx-to-OTC Switch or OTC application: N/A

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

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

Clinical

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

Chemistry

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

- Establishment Evaluation Request (EER) submitted to DMPQ? YES x NO ☐
- If a parenteral product, consulted to Microbiology Team? N/A YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/10/08

NDA #: 22-362

DRUG NAMES: Welchol (colesevelam) (b) (4) for Oral Suspension

APPLICANT: Daiichi Sankyo

BACKGROUND: This is a new formulation of an already approval tablet (NDA 21-176) and capsule (NDA 21-141, never marketed) formulations that were approved 5/26/2000.

ATTENDEES: Eileen Craig, MD
Sally Choe, PhD
Luke Bi, PhD
Su Tran, PhD
Yvonne Yang, PhD
R. Bloom, PhD
Kati Johnson

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

Discipline/Organization	**Reviewer**
Medical:	E. Craig (labeling only)
Secondary Medical:	E. Colman
Statistical:	N/A
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemistry:	Yvonne Yang
Environmental Assessment (if needed):	R. Bloom
Biopharmaceutical:	L. Bi
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
OPS:	Suong Tran
Regulatory Project Management:	Kati Johnson
Other Consults:	

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

CLINICAL FILE x REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO x

If no, explain: No clinical studies

- Advisory Committee Meeting needed? YES, date if known _____ NO x

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

N/A x YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	x	FILE	☐	REFUSE TO FILE	☐	
STATISTICS	N/A	x	FILE	☐	REFUSE TO FILE	☐	
BIOPHARMACEUTICS			FILE	x	REFUSE TO FILE	☐	

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

PHARMACOLOGY/TOX	N/A	x	FILE	☐	REFUSE TO FILE	☐	

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY			FILE	x	REFUSE TO FILE	☐	

- Establishment(s) ready for inspection? YES x NO ☐
- Sterile product? YES ☐ NO x

  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

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

☐ The application is unsuitable for filing. Explain why:

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

☐ No filing issues have been identified.

x Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.x Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. N/A If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. N/A If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. x If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

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

Kati Johnson
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(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.)

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

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

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

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

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

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

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

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

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

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

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

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

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

*If "**No**," skip to question 3.*

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

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

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

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

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

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

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

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

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

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

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

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

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

☐ Not applicable (e.g., solely based on published literature. See question # 7

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

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

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

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

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

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

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

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

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

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Kati Johnson
11/12/2008 06:39:19 AM
CSO