

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-362

CHEMISTRY REVIEW(S)

NDA 22-362

**Welchol™
(colesevelam HCl)
for Oral Suspension**

Daiichi Sankyo, Inc.

**Elsbeth Chikhale, Ph.D.
ONDQA – DPA I – Branch II
for
Division of Metabolism and Endocrinology Products**

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Chemistry Review Data Sheet

1. NDA 22-362
2. REVIEW #: 1
3. REVIEW DATE: 10-JUN-2009
4. REVIEWER: Elsbeth Chikhale, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	15-AUG-2008
Amendment to original ¹	08-DEC-2008
Amendment to original ²	30-APR-2009
Amendment to original ³	14-MAY-2009

- 1) The 8/12/08 amendment provides for updated stability data and a statement of compliance with USP<467>.
- 2) The 4/30/09 amendment provides for a response to an information request from the Agency dated 4/16/09.
- 3) The 5/14/09 amendment provides for a response to an information request made during a teleconference between the applicant and the Agency on 5/8/09.

7. NAME & ADDRESS OF APPLICANT:

Name:	Daiichi Sankyo, Inc.
Address:	399 Thornall Street 10 th floor Edison, NJ 08837
Representative:	Paulette Kosmoski, Executive Director, US/EU & Regional Regulatory Affairs-CMC
Telephone:	(732) 590 – 4875

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Welchol™
- b) Non-Proprietary Name (USAN): Colesevelam HCl
- c) Code Name/#: CAS 182815-44-7
- d) Chem. Type/Submission Priority:
 - Chem. Type: 3 (new dosage form)
 - Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION:** This NDA is submitted as a 505(b)(1) application. The reference listed drug is Welchol (colesevelam HCl) Tablets (NDA 21-176).

10. **PHARMACOL. CATEGORY:** colesevelam is a bile acid sequestrant

11. **DOSAGE FORM:** for Oral Suspension

Note: originally the proposed dosage form was (b) (4) for Oral Suspension”, however, per recommendation from DMEPA (see review in DFS dated 4/28/09) the dosage form was changed to “for Oral Suspension” in order to be consistent with USP.

12. **STRENGTH/POTENCY:** 1.875 g colesevelam HCl/packet and 3.75 g colesevelam HCl/packet

13. **ROUTE OF ADMINISTRATION:** oral

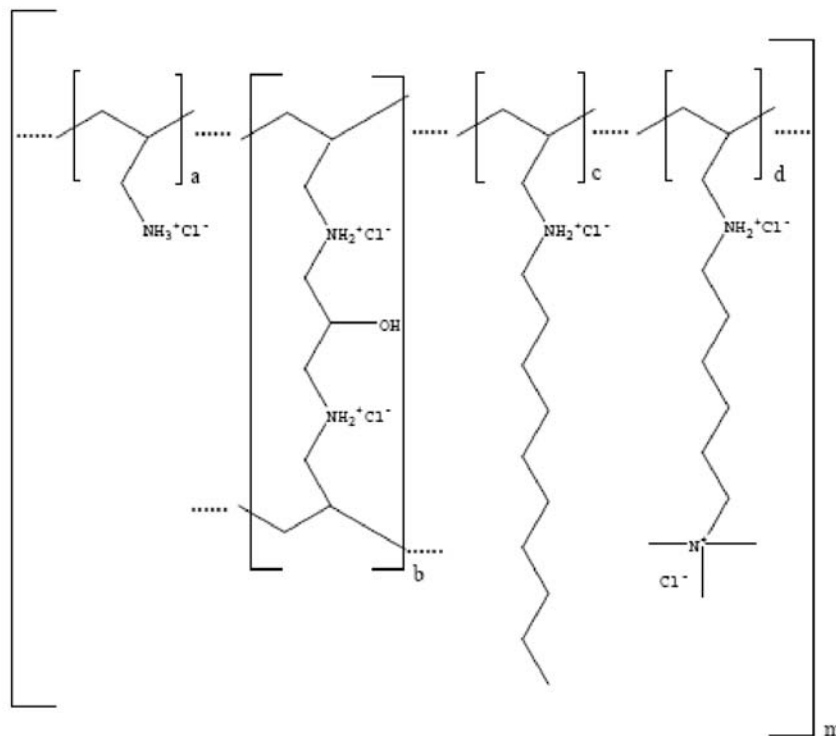
14. **Rx/OTC DISPENSED:** Rx OTC

15. **[SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)**

SPOTS product Form Completed
 Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Where:

- a: number of primary amine groups (a = 0.14)
 b: number of cross-linked amine groups (b = 0.12)
 c: monoquat alkylated amine groups (c = 0.34)
 d: decylbromide alkylated amine groups (d = 0.40)
 m: > 100 to indicate extended polymer network

The structure of colesevelam hydrochloride can be represented as a tetrapolymer of allylamine, N-decylallylamine, N-(6-trimethylammoniumhexyl) allylamine and N,N'-diallyl-1,3-diamino-2-hydroxypropane.

Because colesevelam HCl is a cross-linked polymer,

(b) (4)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	April 19, 2009	Reviewed by Elsbeth Chikhale, Ph.D.
(b) (4)	III	(b) (4)	(u) (4)	4	N/A		
(b) (4)	II	(b) (4) (b) (4)	(u) (4)	1	Adequate	June 1, 2009	Reviewed by Elsbeth Chikhale, Ph.D.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no relevant revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	48,034	Colesevelam HCl, Tablets
IND	68,466	Colesevelam HCl, Tablets

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	6/1/09	
Pharm/Tox	N/A		
CDRH	N/A		
Clinical Pharmacology	Acceptable	6/8/09	Jaya Vaidyanathan, Ph.D.
Methods Validation	Acceptable	8/29/09	Elsbeth Chikhale, Ph.D.
DMEPA	See review in DFS	4/28/09	
EA	Finding of No Significant Impact (FONSI) See review in DFS	4/27/09	Raanan Bloom, Ph.D.
Microbiology	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 22-362

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for APPROVAL.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

1) Drug Product

The proposed formulation (for Oral Suspension) is an alternate dosage form of colesevelam hydrochloride to the approved tablet and capsule formulations (NDA 21-176 and NDA 21-141, respectively). It is a powder for oral suspension. The powder is manufactured by mainly (b) (4)

(b) (4) Specifications for the drug product include: appearance, identification, bile acid binding capacity, label claim, uniformity of dosage units, (b) (4) related substances, and microbial limits. This NDA is submitted electronically as a 505(b)(1). *In vitro* bioequivalence (BE) between Welchol™ (colesevelam hydrochloride) for Oral Suspension and the commercial Welchol™ (colesevelam hydrochloride) Tablets has been demonstrated. It was shown that Welchol powder can be considered to be similar to Welchol tablets in terms of its binding characteristics (see review by Jaya Vaidyanathan Ph.D. dated 6/8/09). In addition, the amount of bile acids bound and the percent bound for the two formulations, was comparable (see review by Jaya Vaidyanathan Ph.D. dated 6/8/09). The proposed formulation/drug product consists of 2 strengths: 3.75 gram colesevelam HCl/packet and 1.875 gram colesevelam HCl/packet. The drug product batches manufactured to support this NDA include registration batches manufactured at the (b) (4) facility and demonstration batches manufactured at the (b) (4) facility. Equivalency between the two manufacturing sites has been demonstrated. The proposed drug product is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia, and adjunctive therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The container closure system is a single use unit-dose packet. The packet has been demonstrated to comply with USP <671> requirements for

transmission of water vapor. The proposed storage condition is at room temperature (25 °C, excursion permitted from 15 to 30 °C), and the proposed expiry date is 24 months for the drug product. The provided stability data support the proposed shelf life of 24 months when stored at room temperature conditions.

2) Drug Substance : Colesevelam HCl:

The drug substance, colesevelam HCl, is a highly cross-linked polymer. It is the same active ingredient of two approved drug products (NDA 21-141 and NDA 21-176). It is a white to off-white powder. It is insoluble in all tested aqueous and organic solvents. Colesevelam is a bile acid sequestrant indicated as an adjunct to diet and exercise to:

- reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia as monotherapy or in combination with an hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor.
- improve glycemic control in adults with type 2 diabetes mellitus.

For all information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of colesevelam HCl, reference is made to approved NDA 21-141 and NDA 21-176. Specifications for the drug substance include: appearance, identification, bile acid binding capacity, (b) (4) (b) (4) organic volatile impurities, related substances, residue on ignition, heavy metals, residual allylamine, soluble oligomers, particle size distribution, particle size, total titratable amines, and microbial limits.

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

The recommended dose is one 3.75 gram packet once daily or one 1.875 gram packet twice daily. To prepare, empty the entire contents of one packet into a glass or cup. Add 4.8 ounces of water. Stir well and drink. Welchel for Oral Suspension should be taken with meals. To avoid esophageal distress, Welchel for Oral Suspension should **NOT** be taken in its dry form.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation from the standpoint of chemistry, manufacture and controls is APPROVAL based on:

- Acceptable drug substance quality
- Acceptable drug product quality
- Drug product stability data to support the proposed shelf life of 24 months
- Acceptable overall recommendation from the Office of Compliance

III. Administrative

A. Reviewer's Signature: in DFS

B. Endorsement Block: in DFS

C. cc Block: in DFS

(D) 52 pages of CMCRev! has been withheld immediately following this page as B4 CCI/TS

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/s/

Elsbeth Chikhale
6/10/2009 03:44:53 PM
CHEMIST

Ali Al-Hakim
6/10/2009 03:48:23 PM
CHEMIST

NDA 22-362

Welchol™ (colesevelam HCl) for Oral Suspension

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

- Applicant:** Daiichi Sankyo, Inc.
399 Thornall Street 10th floor
Edison, NJ 08837
- Indication:** as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia, and adjunctive therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Presentation:** The drug product will be available in a single use unit-dose packet. The recommended dose is one 3.75 gram packet once daily or one 1.875 gram packet twice daily. The entire content of one packet is emptied into a glass or cup. Add 4.8 ounces of water. Stir well and drink.
- EER Status:** Recommendations: Acceptable
- Consults:**
- | | |
|------------------------|--------------------------------|
| EA - | Categorical exclusion provided |
| CDRH- | N/A |
| Statistics - | N/A |
| Methods Validation - | Not recommended |
| Clinical Pharmacology- | Acceptable |
| Microbiology - | N/A |
| Pharm/toxicology - | Acceptable |
- Original Submission:** 15-August-2008
- Re-submissions:** N/A
- Post-Approval CMC Agreements:** None beyond the typical stability commitments.

Background:

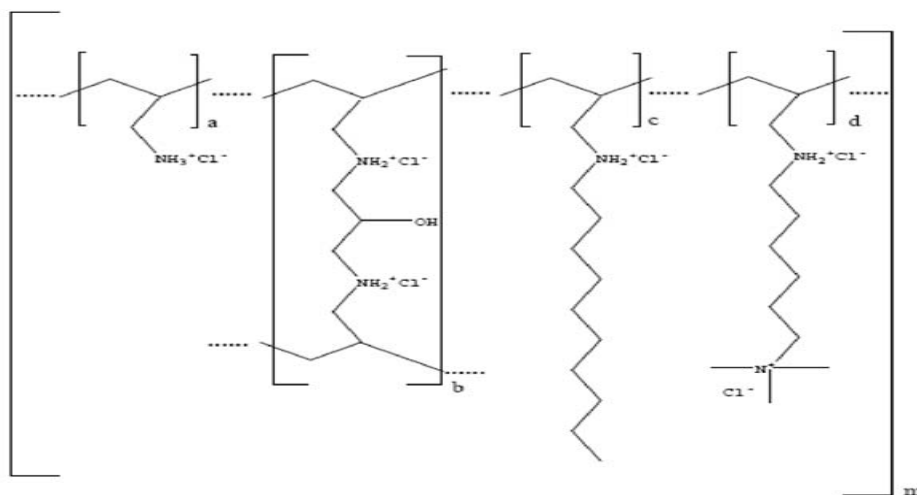
This NDA is submitted as a 505(b)(1) based on the approved tablet and capsule formulations of colesevelam hydrochloride (NDA 21-176 and NDA 21-141,

respectively). The proposed formulation (Oral Suspension) is an alternate dosage form.

Drug Substance:

The drug substance, colesevelam HCl, is a highly cross-linked polymer. It is the same active ingredient of the two approved drug products (NDA 21-141 and NDA 21-176).

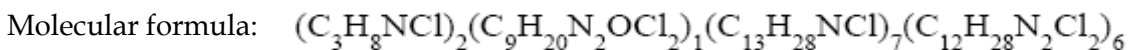
Chemical structure, molecular formula chemical name and molecular weight are provided below.



Where:

- a: number of primary amine groups (a = 0.14)
- b: number of cross-linked amine groups (b = 0.12)
- c: monoquat alkylated amine groups (c = 0.34)
- d: decylbromide alkylated amine groups (d = 0.40)
- m: > 100 to indicate extended polymer network

The structure of colesevelam hydrochloride can be represented as a tetrapolymer of allylamine, N-decylallylamine, N-(6-trimethylammoniumhexyl) allylamine and N,N'-diallyl-1,3-diamino-2-hydroxypropane.



Additional Physical and Chemicals properties.

Colesevelam hydrochloride is a white to off-white ^{(b) (4)} powder with a slight characteristic amine odor. The amines are present predominantly as ammonium salts. Because it is a cross-linked polymer, each particle is one molecule due to multiple covalent cross-links between polymer chains. The polymer is hydrophilic but insoluble in all tested aqueous and organic solvents.

^{(b) (4)}

Information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container

closure system and stability of colesevelam HCl, is provided by reference to the approved NDA 21-141 and NDA 21-176. Specifications for the drug substance include:

appearance, identification, bile acid binding capacity, (b) (4)
(b) (4) organic volatile impurities, related substances, residue on ignition, heavy metals, residual allylamine, soluble oligomers, particle size distribution, particle size, total titratable amines, and microbial limits

Conclusion: The drug substance is satisfactory.

Drug Product:

The proposed formulation (for Oral Suspension) is an alternate dosage form of colesevelam hydrochloride to the approved tablet and capsule formulations (NDA 21-176 and NDA 21-141, respectively); it is a powder for oral suspension.

(b) (4)
Specifications for the drug product include: appearance, identification, bile acid binding capacity, label claim, uniformity of dosage units, (b) (4), related substances, and microbial limits.

In vitro bioequivalence (BE) between Welchol™ (colesevelam hydrochloride) for Oral Suspension and the commercial Welchol™ (colesevelam hydrochloride) tablets has been demonstrated. It was shown that Welchol powder can be considered to be similar to Welchol tablets in terms of its binding characteristics. The proposed formulation/drug product consists of 2 strengths: 3.75 gram colesevelam HCl/packet and 1.875 gram colesevelam HCl/packet. The drug product batches manufactured to support this NDA include registration batches manufactured at the (b) (4) MO facility, however, demonstration batches manufactured at the (b) (4), GA facility. Equivalency between the two manufacturing sites has been demonstrated.

The proposed storage condition is at room temperature (25 °C, excursion permitted from 15 to 30 °C), and the proposed expiry date is 24 months for the drug product. The provided stability data support the proposed shelf life of 24 months when stored at room temperature conditions.

Conclusion: The drug product is satisfactory.

Overall Conclusion: From a CMC perspective, the application is recommended for approval.

Ali Al-Hakim, Ph.D.
Branch Chief,
DPA I/ONDQA

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this page is the manifestation of the electronic signature.**

/s/

Ali Al-Hakim
6/11/2009 05:37:44 PM
CHEMIST

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

See Discussion under Critical Issues.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CRITICAL ISSUES

- **Has all information requested during the IND phases, and at the pre-NDA meetings been included?** Yes. The NDA includes some information as requested by FDA during the IND development. However, there is no direct item-by-item response to FDA's questions, which makes it difficult to assess, for the purpose of this filing memo/IQA, whether the applicant has provided a satisfactory response to each question. The primary reviewer will assess the information in the NDA and decide whether each question has been satisfactorily addressed.

The 19-MAR-2008 Pre-NDA meeting minutes are copied on the next pages. [Note: Question 8 was addressed by the Clinical Pharmacology team.]

Other issues identified during the IND phases:

- Since the drug substance is an insoluble polymer that would be expected to partition to wastewater treatment plant biosolids, FDA recommended on 18-JAN-2008 that land-applied biosolids and toxicity studies in terrestrial organisms be performed. An updated Environmental Assessment is included in the NDA and has been consulted to Dr. R. Bloom of OPS for review.
- On 30-AUG-2004 FDA requested that a complete drug product package be included in the NDA for the new dosage form and that this dosage form be called (b) (4) for oral suspension". Information is provided in the NDA as requested by FDA.

:

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

6. A petition is filed to the CPSC to request an exemption be granted for special packaging requirements for the drug product. In the interim, the registration stability study monitors drug product packaged in both child resistant and nonchild resistant packages. Based on when the CPSC decision is received we plan to discontinue monitoring of one of the packaging systems in the ongoing real time stability study. However, the duration of the stability monitoring will continue to the time point of the FDA assigned expiry period has been reached for the involved packaging system. Is this acceptable to the Agency?

FDA Preliminary Response: Yes, we agree with your proposal to discontinue the stability study of the packaging configuration that will not be part of the commercial product, and that an amendment submitted during the NDA review cycle for this specific stability protocol modification will not extend the review clock.

Teleconference Discussion: None

7. As the registration batch size is identical to the planned commercial batch size, we propose the extension of the drug product expiry date be based on the registration batches real time stability data. Does the Agency agree with this approach?

FDA's Response: Yes, we agree with your proposal to submit a CBE-30 supplement for the expiration period extension based on full long-term data of the registration batches.

Teleconference Discussion: None

8. The approach to demonstrate bioequivalence between the tablet and powder dosage forms will utilize *in vitro* binding assays of bile salts. The powder analysis samples are taken from the 2.5 g fill size pouch for the equilibrium study and from the 5 g fill size pouch for the kinetics study. Is this acceptable to the Agency?

FDA Preliminary Response: Yes, your approach utilizing *in vitro* binding assay of bile salts is acceptable for demonstrating bioequivalence. Provide, in the NDA, why you are using different fill size pouch samples for each study (i.e., equilibrium study vs. kinetics study).

Teleconference Discussion: The firm said there was an error in the meeting background package. Both the equilibrium study and the kinetics study used the same size (5.0 grams) pouch. Therefore, the explanation requested above for why different fill size pouch samples were used is not longer necessary.

9. The registration batches were produced in (b) (4) site facility and the intended commercial production site is the firm's (b) (4) site facility. Batches of drug product made at the (b) (4) location used equipment, processes, procedures the same as or equivalent to the (b) (4) facility. We wish to confirm the approach to providing information/data content in the application to represent the (b) (4) location is acceptable to the Agency.

FDA Preliminary Response: Yes, we agree with your proposal to submit in the initial NDA submission 12 months of long-term stability data and 6 months of accelerated data for the (b) (4) registration batches and to amend the NDA with 3 months of stability data for the (b) (4) batches, provided that you submit this specific amendment prior to month 5 of the review cycle in order to prevent an extension of the review clock.

Teleconference Discussion: The sponsor confirmed that any stability data will be submitted by month 5 of the review cycle. They will notify the Agency prior to submission.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

10. There are 2 fill size package presentations for the powder drug product. Specifically, the 2.5 g pouch contains the dose equivalence to 3 Welchol tablets 625 mg and correspondingly the 5 g pouch contains the dose equivalence to 6 Welchol tablets. The batch size of the registration batches manufactured under production conditions is (b) (4) which is the planned commercial scale in the application. Therefore, we believe the requirement to manufacture (b) (4) of the largest lot planned for full production or a minimum of (b) (4) has been satisfied by the fact that the registration batches and planned commercial batch sizes are identical. Does the Agency concur?

FDA Preliminary Response: Our comment in the 30-AUG-2004 letter "... the test batch or lot of the sachet formulation must be manufactured under production condition and must be of a size at least (b) (4) of the largest lot planned for full production or a minimum of (b) (4) whichever is larger" refers to the batch(es) used in the in vitro bioequivalence study. If one or more of your registration batches was used in this study, then our requirement has been met.

Additional comment: We note your comments on page 48 of the briefing package regarding the planned change in production scale, from the current (b) (4) (to be packaged into (b) (4) batch) to the future (b) (4) (to be packaged into one batch). We agree with your proposal to amend the NDA with 3 months of stability data for the (b) (4) commercial batches, provided that the data will be for at least one batch of each dosage strength (or fill size) and that you submit this specific amendment prior to Month 5 of the review cycle in order to prevent an extension of the review clock.

Teleconference Discussion: The firm clarified that the (b) (4) to be packaged will be in addition to the (b) (4) to be packaged, and they intend to submit information on both the (b) (4) and the (b) (4) within the timeframe requested by the Agency.

11. Is the approach of providing a copy of a single executed batch record for each pouch fill size (i.e., 2.5 g and 5 g) of drug product acceptable to the Agency?

FDA Preliminary Response: Yes, we agree that a copy of the executed batch record(s) for one batch of each dosage strength (or fill size) will be adequate, provided that the batches were used in the primary stability study or in the bioequivalence study as per 21 CFR 314.50(d)(1)(ii)(b).

Additional general comment: We note that your proposed drug product specifications are similar to those of Welchol Tablets, with modifications only for the physical and compositional differences. We recommend that you add testing for attributes specifically relevant to the new dosage form, such as pH for the reconstituted suspension, particle size distribution, redispersibility or suspendability, viscosity, etc., or provide a justification for the lack of such testing. In addition, provide in the NDA a discussion on product-specific degradants because your proposed specification for the powder product has the same identified impurities/degradants found in the tablets.

Teleconference Discussion: None

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CRITICAL ISSUES (continued)

Drug substance

- All CMC information on the drug substance is in the approved and referenced NDAs 21141 and 21176 (same applicant as of the new NDA). Unless new information is submitted in the new NDA, the primary chemist does not need to evaluate the drug substance.

Drug product

- The primary reviewer will assess the information in the NDA and decide whether each question conveyed to the sponsor at the 19-MAR-2008 Pre-NDA meeting has been satisfactorily addressed. [Note: Question 8 was addressed by the Clinical Pharmacology team.]
- The review of the Environmental Assessment has been consulted to Dr. R. Bloom of OPS.
- **Novel excipients.** There are two non-compendial excipients in the drug product: orange/lemon flavoring of (b) (4) and (b) (4) simethicone (b) (4) and (b) (4). The primary reviewer will determine whether the information in the referenced DMFs is adequate to support the use of these excipients. The reviewer will also confirm that the (b) (4) Medium-Chain Triglycerides (b) (4) meets the NF requirements for Medium-Chain Triglycerides (the applicant states that this is a non-compendial excipient but that it is tested for conformance with NF).
- (b) (4) The product is packaged as two strengths: 1.875 g in a 2.65 g packet and 3.750 g in a 5.3 g packet, the active amounts calculated on an anhydrous basis and the fill weights calculated with a moisture content of (b) (4) (b) (4). (b) (4) The primary reviewer will evaluate the moisture content data and determine whether the (b) (4) amounts are justified. The in process control for moisture content is (b) (4). The reviewer will determine whether this test is adequate its purpose or that a more specific test (such as Karl Fischer) should be required.
- **Impurities and degradants.** The applicant claims that there is no new impurity introduced by the new formulation and refers to the approved NDAs 21141 and 21176 for information on the impurity characterization. The limit for unidentified impurities is (b) (4) each, which follows the ICH identification and qualification threshold of 0.05% for a maximum daily dose of 2 g or greater.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

- **Microbial limits.** The powder product has a limit of (b) (4) and Microbial Limits of (b) (4) total aerobic microbial count, (b) (4) molds and yeasts, and absent E. coli. A consult request to Microbiology is not necessary. As per the Microbiology Team Leader's email (see attached at the end of this review), James McVey, the primary reviewer will confirm that the specification includes the absence of E. coli and the test methods are as per USP <61> and <62>. The proposed specification in the NDA does include the absence of E. coli, and the test method is stated to be a "clarification" of USP <61> and <62>.
- **Stability of the drug product.** For filing, the NDA includes 12-month data at 25 °C/60% RH and 6-month data at 40 °C/75% RH for a total of (b) (4) packaged batches (i.e., (b) (4) batches of each dosage strength, each batch packaged in both the child-resistant and (b) (4) pouch). These batches were manufactured at the site in (b) (4) which is not the commercial manufacturing site. As agreed at the Pre-NDA meeting, an amendment will be submitted before Month 5 of the review cycle for 3-month data under both long term and accelerated conditions for an additional (b) (4) packaged batches that were manufactured at the (b) (4). The additional data will bridge the differences between the two manufacturing sites (b) (4). (b) (4) Note that the manufacturing equipment remains the same between the sites because it was moved from (b) (4) to (b) (4). (b) (4) The primary reviewer will compare the two sets of data, evaluate any trending, and determine an expiry based on all available data that best represent the commercial product's stability profile. The reviewer will also determine the in-use shelf life of the reconstituted suspension, based on the in-use data, and evaluate the photostability data of the product. Labeling will also be evaluated to ensure accurate instructions for storage of the powder product as well as the reconstituted suspension.
- **Container closure components.** Reviews of the packaging DMFs may not be necessary if the reviewer finds the information included in the NDA on the safety and suitability of the product-contact components adequate. The NDA includes references to the 21 CFR food additive regulations for the drug-contact components of the container closure systems used to package the product.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Supporting NDA or IND:
NDAs 21141 and 21176

Supporting DMF:

DMF	TYPE	HOLDER	ITEM REFERENCED	LOA
(b) (4)	IV	(b) (4)	(b) (4)	X
	III	(b) (4)		X
	IV	(b) (4)		X

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

GMP facilities: EER was sent to the Office of Compliance on 11-SEP-2008

[Note: the tester of excipients was not included in the EER because the system does not have such function.]

Manufacture of Drug Substance

(b) (4)

Facility function is the manufacturing, packaging and control of the active pharmaceutical ingredient.

Site is ready for inspection and the contact is:

(b) (4)

Manufacturer of Drug Product

(b) (4)

Facility function is manufacturing and packaging of the drug product, release of drug substance, excipients and packaging materials.

Site is ready for inspection and the contact is:

(b) (4)

(b) (4)

Facility function is the analysis of the drug substance and drug product, stability storage and analysis of the drug product.

Site is ready for inspection and the contact is:

(b) (4)

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		All facilities are listed.
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?			Not applicable for CTD format.
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	Not applicable.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

From: McVey, James
Sent: Thursday, September 11, 2008 7:57 AM
To: Johnson, Kati
Cc: Hussong, David
Subject: RE: please ask Microbiology about NDA 22-362 colesevelam HCl

The limits proposed are O.K. but they need to have absence of *E. coli*. They should state that they are testing according to USP <61> and USP <62> and specify what method they have standardized in their laboratory for quantitation (i.e. plate count, filtration, most probable number (MPN)).

From: Johnson, Kati
Sent: Wednesday, September 10, 2008 12:44 PM
To: McVey, James
Subject: FW: please ask Microbiology about NDA 22-362 colesevelam HCl

Hi Jim, could you address the e-mail below. Happy to consult the NDA to you if appropriate. I just came in on 8/14/08
thanks very much,
Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone-301-796-1234
Fax-301-796-9718
Kati.Johnson@fda.hhs.gov

From: Tran, Suong T
Sent: Wednesday, September 10, 2008 12:35 PM
To: Johnson, Kati
Cc: Yang, Yvonne W
Subject: please ask Microbiology about NDA 22-362 colesevelam HCl

Hi Kati!

Please check with your contact in Microbiology to see if they'd want to get a consult request for this NDA 22-362 Welchol (b) (4) for Oral Suspension.

Issue: The powder product has a (b) (4) and Microbial Limits of (b) (4) total aerobic microbial count, (b) (4) molds and yeasts, and absent *E. coli*.

The powder (2.65 g or 5.3g) is suspended in water for oral administration.

Question: Does Microbiology find these limits adequate for this kind of product or would Microbiology like a formal consult request for the NDA review?

Thanks very much!

Su

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

/s/

Suong Tran
10/7/2008 03:43:28 PM
CHEMIST

as we discussed

Ali Al-Hakim
10/7/2008 03:48:49 PM
CHEMIST