CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210895Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: APPROVAL

NDA 210895
Review 2

1. NDA 210-895

Drug Name/Dosage Form	Welchol (Colesevelam hydrochloride) chewable bars chocolate, strawberry and caramel flavors
Strength	3.75 grams/individually packaged bar
Route of Administration	Oral
How Dispensed	Rx
Applicant	Daiichi Sankyo

2. REVIEW #2 (Complete Response) REVIEW DATE: (see last page)

3. QUALITY REVIEW TEAM:

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Product	Anne Marie Russell, Ph.D. ONDP/DNDPII/Branch VI	Danae Christodoulou, Ph.D. ONDP/DNDPII/Branch VI
Facilities	Michael Klapal OPF/DIA III	Ruth Moore, Ph.D.
Regulatory Business Process Manager (RBPM)	Leeza Rahimi, Pharm.D. OPRO	
Application Technical Lead	Anne Marie Russell, Ph.D.	Danae Christodoulou, Ph.D.

4. REGULATORY HISTORY: This is the second review cycle. N 210-895 was originally filed in 30-Oct-2017 and was not approved for CMC/facility issues.

5. SUBMISSION(S) REVIEWED:

Document	Document Receipt Date	DARRTS SDN	Contents
Complete Response (Resubmission Class 2)	03-Oct-2018	20	Complete response to CR letter
Quality Amendment	28-Feb-2019	23	Labeling
Quality Amendment	04-Mar-2019	24	Response to CMC Comments

7. CONSULTS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Facility	Approve	7-Feb-2019	Michael Klapal

Quality Review of Chemistry, Manufacturing and Controls for Division of Metabolism and Endocrinology (DMEP)

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
From a Chemistry, Manufacturing and Controls standpoint, including facility inspection and labeling, this New Drug Application is recommended for approval. A product expiry of 18 months at 25°C/60% RH is granted for all three flavors of individually wrapped chewable bars (chocolate, caramel and strawberry) packaged in the (b) (4) wrappers.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management:
See review.

II. Summary of Quality Assessment

A. Product Overview: See CMC review #1 in Panorama 17-May-2019 Su (Suong) Tran, Ph.D. This is a 505(b)1 application for a new dosage form of an approved drug, colesevelam hydrochloride. The active ingredient has several approved NDAs.

B. Product Quality Assessment Overview: In review cycle #1, the applicant was issued a Complete Response letter on 24-Aug-2018, which cited facilities deficiencies. In this review cycle, #2, the applicant addressed the facility deficiencies and submitted stability data for the commercial lots - see Section III below.

C. Life Cycle Knowledge Information: The submitted manufacturing history of the commercial product is limited (b) (4). In the Post-Approval Stability Protocol and Commitment the applicant will monitor additional stability attributes (wrapper seal integrity and microbial contamination from Bile-Tolerant Gram-Negative) in the validation and future commercial lots.

D. Final Risk Assessment: (see Attachment at end of review)

III. Review of Applicant's Response to CMC Deficiencies:

1. FACILITY INSPECTION

After review cycle#1, a Complete Response letter was issued on 24-Aug-2018 and cited the following Product Quality deficiency:

"During a recent inspection of the (b) (4) drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

Assessment: See Facilities review in Panorama dated 25-Feb-2019. The drug product is manufactured at (b) (4) under an agreement with Daiichi. The facility was re-inspected in (b) (4) and the facility reviewer issued a recommendation to approve on 7-Feb-2018 (see Appendix). In brief, the inspector found that the firm's investigation into their root cause of microbial contamination in the product and their subsequent controls ((b) (4).) were acceptable. The Drug Product Specifications now include an additional microbial limit test for "Bile-tolerant Gram-Negative" with an acceptance limit of (b) (4) See updated specifications in the Appendix.

Evaluation: Acceptable risk mitigation and facilities review recommendation for approval.

2. STABILITY DATA

The Complete Response letter included the following additional CMC comment:

"We have the following comment/recommendation that is not an approvability issue:
In the resubmission, provide 24-month stability data for the six registration batches ((b) (4) kg) and all available stability data for the six demonstration batches ((b) (4) kg). "

Response: Daiichi submitted 24 month long term (25°C/60% RH) stability data for the six registration batches. They also submitted 9 month long term and 6 month accelerated (40°C/75% RH) stability data for the six demonstration batches. The registration lots were pilot scale lots manufactured on a (b) (4) The demonstration lots were commercial lots manufactured (b) (4) The demonstration lots are representative of the commercial product.

Assessment: An expiry was not granted in review cycle #1 due to the Complete Response action. There are two issues that arose in the new stability data submitted in the Complete Response – Degradants and Seal Integrity – reviewed below.

Background - In review cycle #1, stability data were submitted for only the registration batches, which were not manufactured on the commercial line. No stability data were submitted for the demonstration batches manufactured on the commercial line. The product showed increasing levels of degradants on stability – as

it is seen in the approved tablet dosage form. The most significant increase was observed in the levels of the degradation product (b) (4), which is controlled to an acceptance criterion of (b) (4) on release and stability. While the product did not exceed (b) (4) threshold under long term conditions, the levels reached (b) (4) at 18 months for the chocolate bar lot# DSIW-125.6034R3B. Further, under accelerated conditions, the chocolate bars failed at 3 months and the caramel bars reached (b) (4)% at 6 months. The strawberry bars showed a much less significant increasing trend for the degradants, but did show a color change (b) (4).

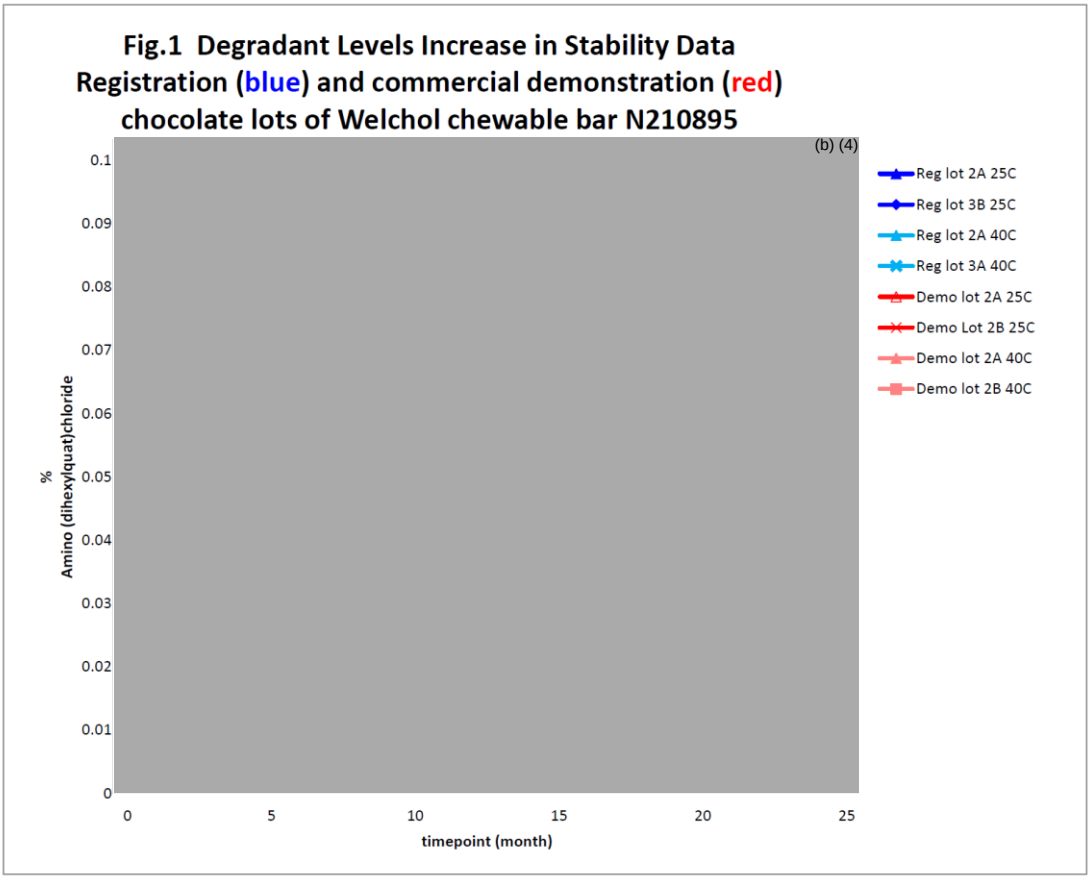
Summary current submission - In this review cycle, #2, new stability data were provided for the registration and demonstration lots submitted in review cycle #1. While the inspection report indicates that 50 batches have been manufactured at (b) (4) (training, development, etc), no additional lots have been submitted to the NDA. The new stability data provided were:

- 24 month timepoint at 25°C for 12 registration finished lots (two (b) (4) kg bulk lots each of chocolate, strawberry and caramel, each split into two sublots which were packaged in (b) (4) and (b) (4) wrappers)
- 0,1,3,6 and 9 month timepoints at 25°C for 12 demonstration finished lots (two (b) (4) kg bulk lots each of chocolate, strawberry and caramel, each split into two sublots which were packaged in (b) (4) and (b) (4) wrappers)
- 0,1,3 and 6 month timepoints at 40°C for the same 12 demonstration finished lots

Stability data were submitted for appearance, bile acid binding capacity, assay, loss on drying, degradation products, microbial limits, hardness, weight, dimension and seal integrity ((b) (4)).

A. Issue: Degradants: Overall, the new stability data in both the registration and demonstration lots show the same trend for the degradation product (b) (4) under accelerated and long term conditions – rapid and mostly linear increase with time for all flavors, with early failure under accelerated conditions. See Figure 1, compiled by this reviewer. The degradant levels exceed the maximum allowed ((b) (4)) under accelerated conditions (40°C) as early as 3 months. The increase is significant ((b) (4) but more gradual at 25°C, with the demonstration lots reaching, but not exceeding, (b) (4)% at 24 months. The increase is most rapid with the chocolate flavor, closely followed by the caramel flavor and the strawberry markedly slower.

Of note in Figure 1, the new 24-month data for the degradation product (b) (4) reaches but does not exceed the acceptance criteria of (b) (4). It does sharply divert from the linear trend as can be seen in Figure 1 below (blue). A plateau is visible in the long-term data at (b) (4) levels for the 18 month and 24 month timepoints, but not in the accelerated data.



B. Issue Seal Integrity: The chewable bar is a new product dosage form for an NDA. A chewable bar was previously approved in an ANDA. It is a 4" long rectangular bar individually wrapped in a foil laminate wrapper, (b) (4) The integrity of this wrapper seal is tested by a vacuum dye test. (b) (4) performed on stability on the registration and demonstration lots, as a "for information only" test.

In review cycle #1, the stability data showed that the registration lot bars all passed the vacuum dye test for seal integrity. At 5 bars per test, with 12 registration lots and 8 long term timepoints and 4 accelerated timepoints, that testing included about (b) (4) bars and reported 100% pass result (0% failure). In the pilot scale manufacturing of these registration finished lots, the bulk lots were split in two and each finished lot was wrapped in a foil wrapper supplied by (b) (4). Equal numbers of (b) (4) wrapped bars and (b) (4) wrapped bars were manufactured. The demonstration finished lots (commercial scale) were also manufactured in equal numbers of (b) (4) wrapped bars, but no stability data were submitted in review cycle #1.

In review cycle #2, initial stability data (9 mos) were submitted for the demonstration lots and the seal integrity test results show markedly worse performance of the package. Of the approximately (b) (4) bars tested, 40 failed seal integrity (~7.4% failure rate) – failures occurred in all flavors, all timepoints, under all

storage conditions and for both types of wrappers [redacted]). See Table 1, compiled by this reviewer.

Table 1. Package issue - wrapper seal integrity failure reported in stability data				
Product lots (all flavors)	**Wrapper manufacturer**	**Total bars tested (estimate)**	**Exact number of bars that failed seal integrity testing (stability data)**	**Approximate % Failure rate (100*failed/total)**
Registration (pilot)	[redacted]	[redacted]	0	0%
			0	0%
Demonstration (commercial)			33	12.2%
			7	2.6%
	Total		40	7.4%

Both registration lots and demonstration lots were packaged in the same two wrappers – [redacted] (sublot A) and [redacted] (sublot B). The change in seal integrity performance between the registration batches and the demonstration (commercial) batches is coincident with a manufacturing change [redacted]. The registration lots, which had no seal failure, were manufactured on [redacted]. The demonstration lots, which had significant seal failure, were manufactured [redacted]). They are more representative of the commercial product.

The failure rates of the two wrappers are very different: 82.5% of the failed wrappers were [redacted] the remaining 17.5% were [redacted] See Table 2, compiled by this reviewer. According to the inspection report, the applicant stated that only the wrapper manufactured by [redacted] will be used for the commercial batch production.

Table 2. Wrapper failure by manufacturer (demonstration lots)		
Wrapper manufacturer	**Number of bars that failed (mfg)**	**% of Total bars that failed (100*mfg/total)**
[redacted]		82.5%
		17.5%
		100%

To address the wrapper failure, the following comments were sent to the applicant on 1-Mar-2019. The response from the applicant, Daiichi, was received by email on 4-Mar-2019.

1. **Provide to the NDA a written commitment to remove (b) (4) as a wrapper supplier.**

   Response:

   Daiichi Sankyo response:

   Daiichi Sankyo commits to remove (b) (4) as a wrapper supplier from the NDA. Subsequently, Section 3.2.P.7 had been revised to remove all information on the (b) (4) wrapper.

   Assessment: Acceptable. The wrappers with the highest number of failures reported on stability for the demonstration lots, manufactured by (b) (4) (82.5%), have been removed from the NDA Container Closure section.

2. **Revise Drug Product specification with Seal Integrity as a test conducted on stability and revise Post-Marketing Stability Protocol to include Seal Integrity and microbial Bile-Tolerant Gram-negative testing. Submit to the NDA.**

   Response:

   Daiichi Sankyo response:

   The drug product specifications have been revised to include Seal Integrity as a test conducted on stability, refer to Section 3.2.P.5.1 for the revised specifications. In addition, the Post-Marketing Stability Protocol has been revised to include Seal Integrity and Microbial Bile-Tolerant Gram Negative testing, refer to Section 3.2.P.8.2 for the revised stability protocol.

   Assessment: Acceptable. To monitor seal integrity in future lots, testing has been added to the drug product specifications on stability and included in the Post-Marketing Stability Protocol. See Appendix.

3. **Provide a Post-Marketing agreement to continue to test seal integrity of your product on stability. Include this test in your post-approval stability protocol. Assess the risk for product degradation and microbial integrity upon validation of commercial production and post-approval stability data on the validation and commercial lots. Submit these data to the NDA to demonstrate successful resolution of the seal integrity failure problem.**

Response:

Daiichi Sankyo response:

As noted above for Response No. 2, the post-approval stability protocol has been revised to include seal integrity testing. Daiichi Sankyo commits to assess the risk of product degradation and microbial integrity upon validation of the commercial product and from the post-approval stability data on validation and commercial lots. Once generated, these data will be submitted to the NDA Annual Report to demonstrate successful resolution of the seal integrity failures observed.

Assessment: Acceptable. The applicant was advised to submit the stability data in a supplement.

The following comment was sent on 6-March-2019:

"We acknowledge and accept your responses of 4-Mar-2019. We advise you to submit your report of stability data from your production batches in a post-approval supplement rather than the annual report."

A clarification, in response to the Applicant's inquiry by email, was sent on 7-Mar-2019:

"The category of the supplement will be determined at the time of submission."

4. **Clarify if the seal integrity failure(s) are visible to the consumer e.g., broken seal, change in appearance of the bar etc.**

Response:

Daiichi Sankyo response:

The wrapped chewable bars that failed seal integrity have no visible broken seals or holes that the consumer can see. There was no change in the appearance of the bars as documented in the stability data.

Assessment: The applicant clarifies that seal integrity failure is not visible to the consumer.

Final Assessment Seal Integrity: From the standpoint of risk to the patient, a Failure Mode, Effects and Criticality Analysis (FMECA) can evaluate the individual factors involved in failed seal wrapper integrity and their controls:

Factors - a failed seal in the packaging of the individually wrapped chewable bar may allow microbial contamination, may change the appearance, may increase degradants or may increase hardness of the bar from water loss. Stability data (0,1,3,6 and 9 months) on the bars with failed seals show that they pass specifications for appearance, degradants and hardness. These data control the risk associated with these factors. As for microbial contamination - at this time there are no data to evaluate this risk as the 9 month stability data on the failed lots did not include microbial testing. However, the stability protocol includes microbial testing at the 12 month timepoint and the applicant has committed to assess the risk for product degradation and microbial integrity upon validation of commercial production and post-

approval stability data on the validation and commercial lots. They also committed to submit these data to demonstrate successful resolution of the seal integrity failure problem.

Detectability – A failed seal is not visible to the consumer – the wrapper does not have visible broken seals or holes and the product appearance is not changed - so the patient cannot see that a bar has a failed seal and discard it. However, a failed seal can be detected on stability by performing the vacuum dye test in the stability program. The applicant has added this test to their drug product specifications for stability and to their post-marketing stability program.

Severity of Effect - the bar is a non-sterile oral product, so the severity impact from microbial contamination is low as compared to a high risk dosage form such as a sterile, injectable product.

Probability – at this time, the likelihood that future lots will be manufactured with faulty wrapper seals is high based on the limited manufacturing experience with the commercial line. Data were submitted for only one commercial production run ((b) (4)), and every lot failed seal integrity on stability testing. However, the likelihood has been controlled with eliminating the (b) (4) wrapper which failed at a much higher rate than the (b) (4) wrapper. The applicant has removed the (b) (4) wrapper from their NDA and will only manufacture with the (b) (4) wrapper. Further, the likelihood can also be controlled with increased manufacturing experience and stability data from future lots. To that end, the applicant has submitted a post-marketing stability program which includes validation and commercial lots. See Appendix Post-Approval Stability Protocol.

Evaluation: Acceptable. Considering the factors, detectability, severity, probability and the controls in place (including post-marketing stability program), the risk associated with failed seal integrity is low at this time and does not impact approvability.

Expiry: In the stability data, here are two significant changes to evaluate for expiry – seal integrity for microbial integrity and degradants. For seal integrity: the registration lots did not fail the seal integrity test on stability. However, the demonstration lots, manufactured at the commercial line, showed seal integrity failure. This is a failure not observed in the registration lots. Therefore, the registration stability batch data cannot be considered fully representative of the commercial drug product performance. For degradants: the registration and demonstration (commercial) lots both failed stability for (b) (4) levels under accelerated conditions. Therefore, extrapolation of shelf life beyond the period covered by long-term data is not appropriate, as per ICH Q1E guidelines. Consequently, based on the limited demonstration (commercial) lot stability data (to 9 months) and the registration lots stability data – including degradation levels and seal integrity failure in the commercial lots - sufficient data were provided to support an 18 month expiry for storage at 25°C/60%RH conditions for all flavors (chocolate, caramel and strawberry) in the (b) (4) wrapper.

The following comment was sent to the applicant on 1-Mar-2019:

5. **An 18-month expiry at 25°C/60% RH condition is granted for your product**.

As a clarification, in response to the Applicant's inquiry by email, the following reply was sent the same day:

(b) (4)

Evaluation: Acceptable with a post-marketing agreement. The stability data supports an 18 month expiry at 25°C/60% R/H conditions for all flavors (chocolate, caramel and strawberry) in the (b) (4) wrapper. The Post-Approval Stability protocol includes testing for wrapper seal failure.

3. LABELING:

The PI and carton and container labeling have been reviewed by CMC with comments (see Table 3 below). At this time, labeling has not yet been finalized by DMEP. The container is an individual wrapper and the carton is a box. There is one trade and one professional sample wrapper for each flavor. There is one trade box for 30 count bars for each flavor. There are two professional sample boxes for 3 count and 6 count. See Appendix.

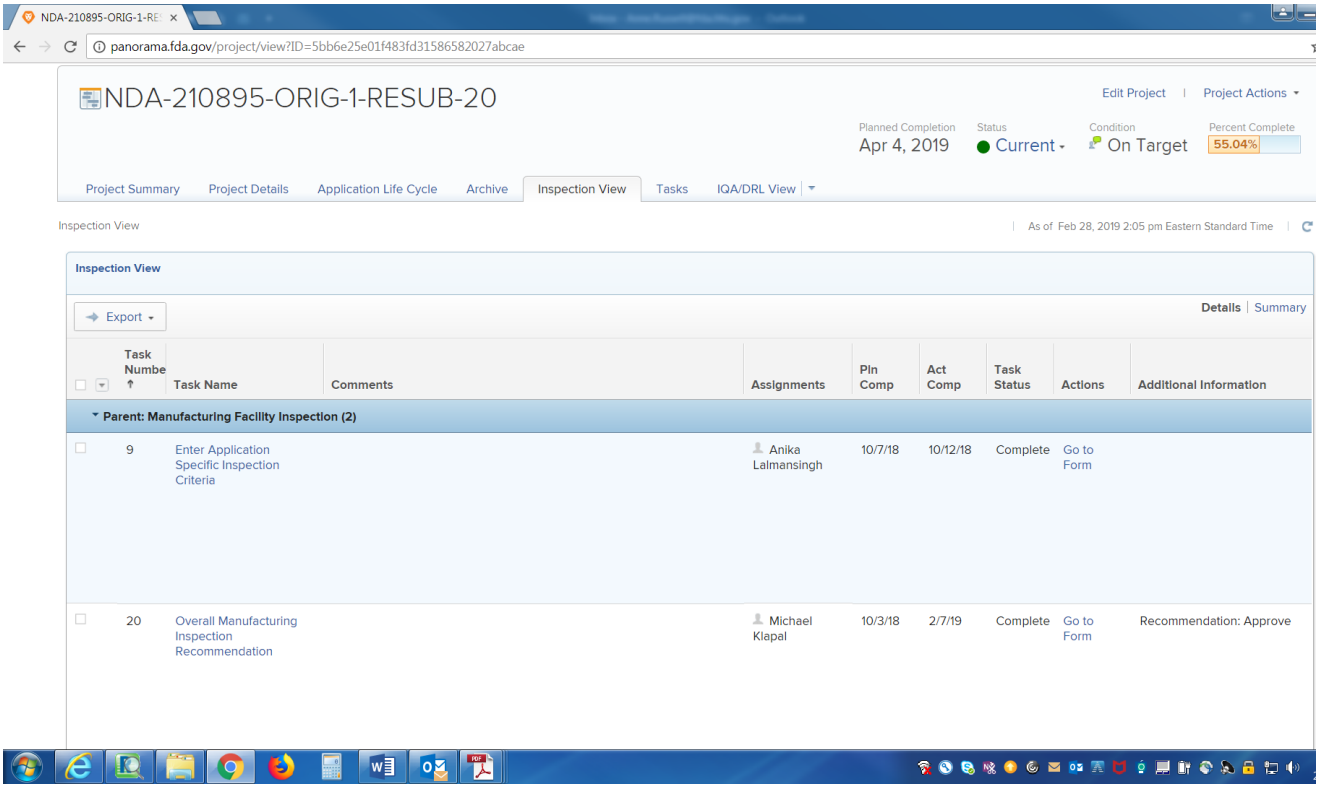
Section	Changed To
PI Highlights	Chewable Bars
PI How Supplied	Individually wrapped (b) (4) bars
Carton (box)	Welchol (colesevelam HCl) Chewable Bars

ATTACHMENT

From Initial Risk Identification			Review Assessment		
Attribute/CQA	**Factors that can impact CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/Comments**
Microbiological attributes	• Facilities (GMP, cleaning, etc) • Product Testing (release and stability)	high	• Reinspection (acceptable) • Increased testing (added Bile-Tolerant Gram-Negative test)	low	none
Packaging - Wrapper seal integrity	• Process • Wrapper supplier	high	• Increased testing of seal integrity • Post-Marketing stability protocol • Eliminated supplier with high failure • Non-sterile oral product (low exposure)	low	Existing initial stability data (9 mos) show all attributes tested are not affected by failed wrapper seal integrity, excluding microbiological attributes which were not yet tested. Risk is controlled with (b) (4) stability testing of validation and production lots manufactured with the (b) (4) wrapper, which had a much lower failure history than (b) (4) Lots will not be manufactured with (b) (4) wrapper. Post-approval stability protocol includes submitting results to demonstrate wrapper integrity problem is resolved.
Impurities/degradants	Formulation, process, container closure	moderate	Stability studies In-process controls	low	Current expiry is limited to 18 months due to degradant levels increasing on stability
Drug Content/Assay	Formulation, process, container closure	low	N/A	N/A	none
Appearance	Formulation, process, container closure	low	N/A	N/A	none
Drug Release Rate	Formulation Process	low	N/A	N/A	none
Content Uniformity	Process	low	N/A	N/A	none

APPENDIX

Screen shot of Panorama page listing the facility recommendation to approve, entered 7-Feb-2019.



Updated Drug Product Specifications submitted 4-Mar-2019 now include an additional testing - microbial limit for Bile-tolerant Gram-negative and seal integrity, as recommended

P.5.1 Control of Drug Product - Specifications
Welchol® (colesevelam hydrochloride) Chewable Bars

Table 1.3: Welchol® (colesevelam hydrochloride) Chewable Bars, Caramel Release and Stability Specification

Test Parameter	Analytical Procedure	Acceptance Criteria
Appearance	Visual	(b) (4)
Identification[a]	Ninhydrin Color Test M12172	
Bile Acid Binding Capacity Glycocholic Acid Sodium Salt Glycochenodeoxycholic Acid Sodium Salt	High Performance Liquid Chromatography (HPLC) M12600	
Assay	Total Amine Titration M12170	
Uniformity of Dosage Units[a]	USP <905> by Titration M12170	
Loss on Drying	USP <891> Thermogravimetric Analysis M12173	
Degradation Products (b) (4) Other unidentified related Total other related	Gas Chromatography (GC) M12403	
Degradation Products (b) (4) Other unidentified related Total other related	Ion Chromatography (IC) M12509	
Microbial Limits Total Aerobic Microbial Count Total Yeasts and Molds Count Bile-Tolerant Gram-Negative *Escherichia coli*	USP <61> and <62> M13150	
Hardness	Texture Analyzer QCT-023	
Seal Integrity Test[b]	Leak Test by Vacuum QCT-021	
(b) (4)		

The Post-Approval Stability protocol has been updated on 4-Mar-2019 to include testing for wrapper seal integrity and Bile-Tolerant Gram-Negative

P.8.2 Postapproval Stability Protocol and Stability Commitment
Welchol® (colesevelam hydrochloride) Chewable Bars

Table 1.1: Welchol® (colesevelam hydrochloride) Chewable Bars: Validation Stability Protocol

Test Parameter (Analytical Procedure)	Acceptance Criteria	Storage Condition	Time Point (Months)										
			0	1	3	6	9	12	18	24	36	48	60
Appearance (Visual)	(b) (4)	25° ± 2°C/60% ± 5% RH	X	X	X	X	X	X	X	X	X	X	X
		30° ± 2°C/65% ± 5% RH[a]		X	X	X	X	X					
		40° ± 2°C/75% ± 5% RH		X	X	X							
Bile Acid Binding Capacity (HPLC) M12600		25° ± 2°C/60% ± 5% RH	X	X	X	X	X	X	X	X	X	X	X
		30° ± 2°C/65% ± 5% RH[a]		X	X	X	X	X					
		40° ± 2°C/75% ± 5% RH		X	X	X							
Assay (Total Amine Titration) M12170		25° ± 2°C/60% ± 5% RH	X	X	X	X	X	X	X	X	X	X	X
		30° ± 2°C/65% ± 5% RH[a]		X	X	X	X	X					
		40° ± 2°C/75% ± 5% RH		X	X	X							
Loss on Drying USP <891> M12173		25° ± 2°C/60% ± 5% RH	X	X	X	X	X	X	X	X	X	X	X
		30° ± 2°C/65% ± 5% RH[a]		X	X	X	X	X					
		40° ± 2°C/75% ± 5% RH		X	X	X							
Degradation Products (GC) M12403		25° ± 2°C/60% ± 5% RH	X	X	X	X	X	X	X	X	X	X	X
		30° ± 2°C/65% ± 5% RH[a]		X	X	X	X	X					
		40° ± 2°C/75% ± 5% RH		X	X	X							
Degradation Products (IC) M12509		25° ± 2°C/60% ± 5% RH	X	X	X	X	X	X	X	X	X	X	X
		30° ± 2°C/65% ± 5% RH[a]		X	X	X	X	X					
		40° ± 2°C/75% ± 5% RH		X	X	X							

Table 1.1: Welchol® (colesevelam hydrochloride) Chewable Bars: Validation Stability Protocol (Continued)

Test Parameter (Analytical Procedure)	Acceptance Criteria	Storage Condition	Time Point (Months)										
			0	1	3	6	9	12	18	24	36	48	60
Microbial Limits USP <61> and <62> M13150	(b) (4)	25° ± 2°C/60% ± 5% RH	X					X		X	X	X	X
Hardness Texture Analyzer QCT-023		25° ± 2°C/60% ± 5% RH	X	X	X	X	X	X	X	X	X	X	X
		30° ± 2°C/65% ± 5% RH[a]		X	X	X	X	X					
		40° ± 2°C/75% ± 5% RH		X	X	X							
Seal Integrity Vacuum Dye Test QCT-021		25° ± 2°C/60% ± 5% RH	X	X	X	X	X	X	X	X	X	X	X
		30° ± 2°C/65% ± 5% RH[a]		X	X	X	X	X					
		40° ± 2°C/75% ± 5% RH		X	X	X							

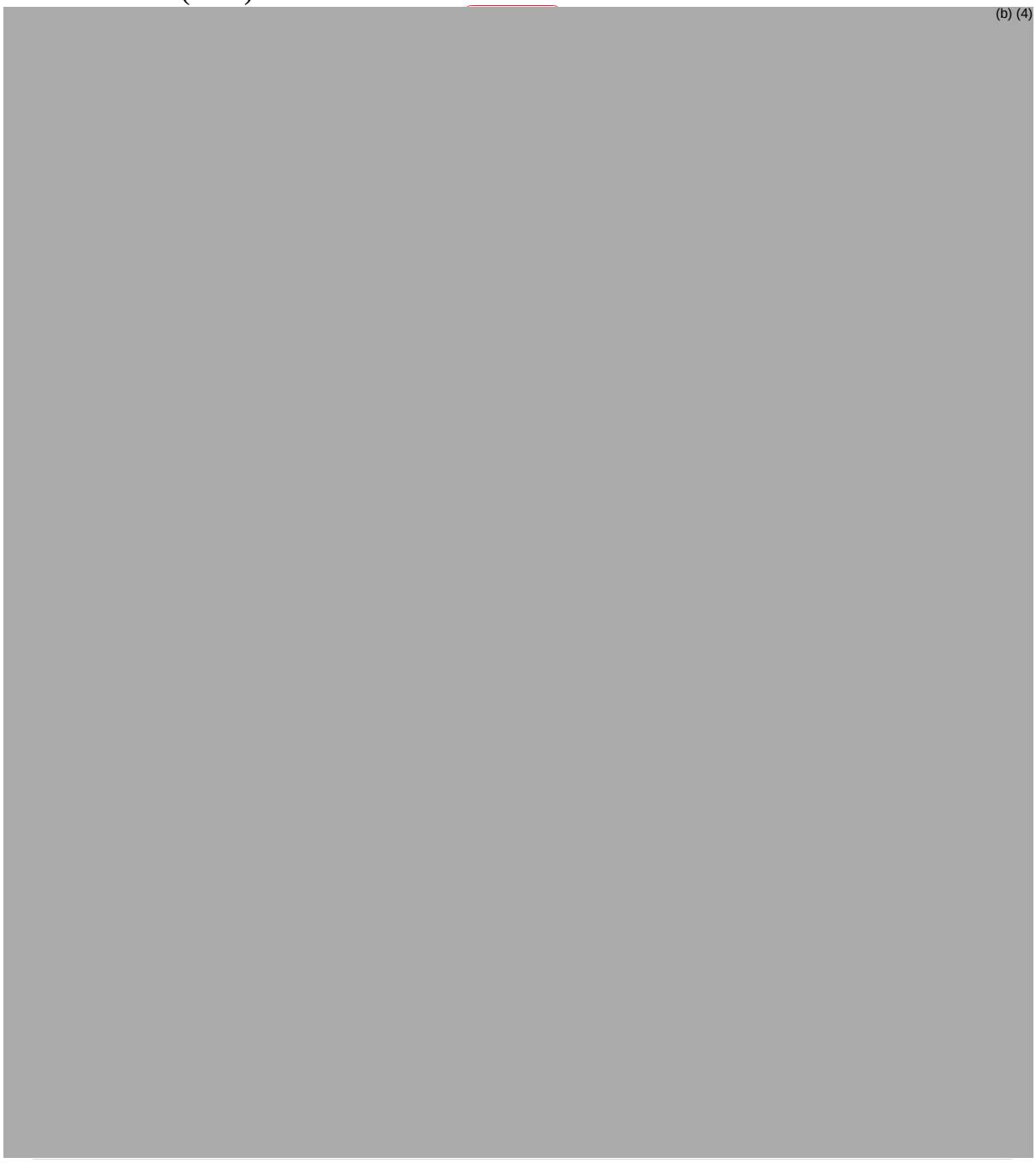
NMT: Not More Than CFU: Colony Forming Units

(b) (4)

Labeling The container is an individual wrapper and the carton is a box.
Examples below

Chocolate

Carton: Box of 30 count (trade):



Batch History of the registration batches manufactured at (b) (4) kg scale on the pilot manufacturing line (2016) and of the demonstration batches manufactured at (b) (4) kg scale on the commercial line (2017).

Table 1.1: Welchol® (colesevelam hydrochloride) Chewable Bars Batch Overview

Flavor	Drug Substance Batch No.	Drug Product Batch No.	Date of Manufacture	Batch Size	Batch Purpose	Release Data
Chocolate	LFCSMB3038-6195	DSIW-125.6034R2A	03 Feb 2016	(b) (4)	Registration Stability	Table 1.2
		DSIW-125.6034R2B				
	LFCSMB3110-6259	DSIW-125.6034R3A	09 Feb 2016			
		DSIW-125.6034R3B				
	LFCSMB4052-6449	DSIW-125.7191DB1	11 Jul 2017		Demonstration Stability	Table 1.3
	LFCSMB4053-6449	DSIW-125.7191DB2	12 Jul 2017			
Strawberry	LFCSMB3110-6259	DSIW-126.6039R1A	08 Feb 2016		Registration Stability	Table 1.4
		DSIW-126.6039R1B				
	LFCSMB3038-6195	DSIW-126.6039R2A	08 Feb 2016			
		DSIW-126.6039R2B				
	LFCSMB4052-6449	DSIW-125.7199DB1	19 Jul 2017		Demonstration Stability	Table 1.5
	LFCSMB4053-6449	DSIW-125.7199DB2	20 Jul 2017			
Caramel	LFCSMB3110-6259	DSIW-127.6032R1A	01 Feb 2016		Registration Stability	Table 1.6
		DSIW-127.6032R1B				
	LFCSMB3038-6195	DSIW-127.6032R2A	01 Feb 2016			
		DSIW-127.6032R2B				
	LFCSMB4052-6449	DSIW-127.7194DB1	17 Jul 2017		Demonstration Stability	Table 1.7
	LFCSMB4053-6449	DSIW-127.7194DB2	18 Jul 2017			

Anne Russell

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Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 3/12/2019 12:09:39PM
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QUALITY REVIEW

Recommendation: COMPLETE RESPONSE
(including the Facility Review/Overall Manufacturing Inspection Recommendation)

NDA 210895

Review #1
Review Date (see last page)

Drug Name/Dosage Form	Colesevelam hydrochloride chewable bar
Strength	3.75 g
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Daiichi Sankyo

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0001	10/30/17
0002	11/13/17
0006	1/22/18
0010	2/15/18
0011	3/9/18
0012	4/6/18
0014	4/24/18
0015	4/25/18
0016	5/10/18

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Lawrence Perez/Donna Christner	New Drug API/ONDP
Drug Product	Anne Marie Russell/ Danae Christodoulou	New Drug Products II/ONDP
Process	Hong Yang/Yong Hu	Process Assessment II/OPF
Facility	Michael Klapal/Vidya Pai	Inspectional Assessment/OPF
Microbiology	Koushik Paul/Erika Pfeiler	Microbiology Assessment/OPF
Environmental Assessment	Raanan Bloom/M. Scott Furness	ONDP

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   - **A. DMFs:** Adequate
     (see Chapter I Drug Substance and Chapter II Drug Product)
   - B. **Other Documents:** From the same applicant- Approved NDAs 21141, 21176, and 22362 for the same drug in different dosage forms (Welchol Tablet, Welchol Capsule, and Welchol for Oral Suspension, respectively)
2. **CONSULTS:** none

Executive Summary

I. Recommendation and Conclusion on Approvability

The final OPQ recommendation is for Complete Response, including the overall manufacturing inspection recommendation.

Summary of Complete Response issue:
(b) (4)) is the proposed commercial drug product manufacturing site. Prior to this NDA, this site was known to FDA as a dietary supplement manufacturer and did not have any inspectional history for human drug manufacture. After the NDA-specific pre-approval inspection of the site (conducted from (b) (4) FDA issued inspection observations. Responses by the site to FDA's observations were found inadequate by FDA. The major issue that has not been resolved involves persistent microbial contamination at the site (see Chapter VI of this review for details).

Action letter language (CR deficiency):
"During the recent inspection of the drug product manufacturing facility (b) (4) our field investigators observed objectionable conditions at the facility and conveyed that information to the representatives of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this application may be approved."

Additional comment (non-approvability issue) to be included in the action letter:

- **In the resubmission, provide 24-month stability data for the six registration batches (b) (4) kg) and all available stability data for the six demonstration batches (b) (4) kg).**

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(1) NDA for colesevelam hydrochloride chewable bar. The product is not an NME because the same applicant has three approved NDAs (21141, 21176, and 22362) for the same drug in different dosage forms (Welchol Tablet, Welchol Capsule, and Welchol for Oral Suspension, respectively).

The drug substance colesevelam hydrochloride is a non-absorbed, water-insoluble polymer functioning as a bile acid sequestrant that lowers total and low-density lipoprotein cholesterol levels.

The drug product is a chewable bar containing 3.75 g of colesevelam hydrochloride, formulated with food ingredients, packaged in a child-resistant foil laminate pouch.

Each bar is 0.33-0.44 inch thick, 3.44-4.13 inch long, and 0.89-1.13 inch wide, and it weighs 28.5-32.5 g. There are three flavors: chocolate, strawberry, and caramel.

Clinically relevant studies submitted in support of the product include an in vitro bioequivalence study with Welchol Tablets and a study of the effects of chewing and digestion on bile acid capacity (reference is made to the Clinical Pharmacology review). The biobatches are also primary stability batches (chocolate 125.6034R3A, strawberry 126.6039R1A, and caramel 127.6032R1A). They were manufactured at the commercial site ((b) (4) at pilot scale (b) (4) kg).

Proposed Indication(s)	Bile acid sequestrant (see the Clinical review)
Duration of Treatment	chronic
Maximum Daily Dose	3.75 g
Alternative Methods of Administration	n/a

A. Quality Assessment Overview

Drug Substance

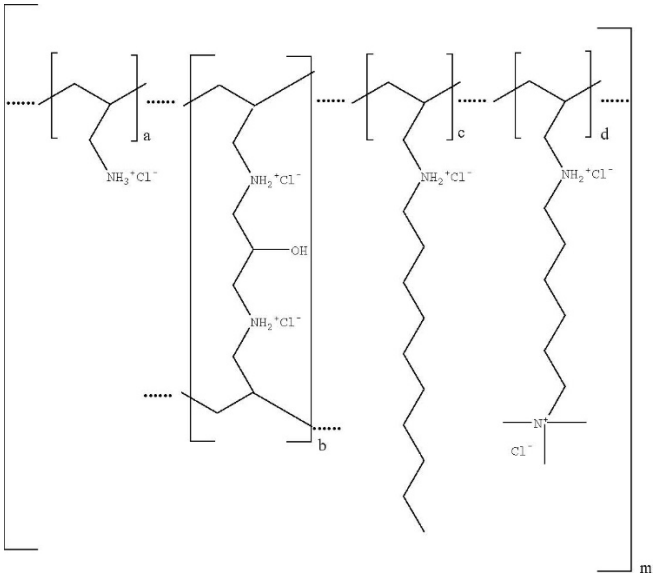
The drug substance colesevelam hydrochloride is a non-absorbed, water-insoluble polymer functioning as a bile acid sequestrant that lowers total and low-density lipoprotein cholesterol levels.

The chemical name (IUPAC) of colesevelam hydrochloride is allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl]trimethylammonium chloride and N allyldecylamine, hydrochloride.

Molecular formula: $(C_3H_8NCl)_2(C_9H_{20}N_2OCl_2)_1(C_{13}H_{28}NCl)_7(C_{12}H_{28}N_2Cl_2)_6$

Molecular weight: 212 g/mol for the tetrapolymer subunit which corresponds to about 0.14 allylamine hydrochloride units, about 0.12 hydroxypropyl units, about 0.34 hexylquat chloride units, and about 0.40 decyl units.

The chemical structure of colesevelam hydrochloride is represented by the following formula:



wherein (a) represents allyl amine monomer units that have not been alkylated by either of the 1 bromodecane or (6-bromohexyl)-trimethylammonium bromide alkylating agents or cross linked by epichlorohydrin; (b) represents allyl amine units that have undergone cross-linking with epichlorohydrin; (c) represents allyl amine units that have been alkylated with a decyl group; (d) represents allyl amine units that have been alkylated with a (6 trimethylammonium) hexyl group, and m represents a number ≥ 100 to indicate an extended polymer network. A small amount of the amines are dialkylated, and are not depicted in the formula above. No regular order of the groups is implied by the structure; cross-linking and alkylation are expected to occur randomly along the polymer chains. A large amount of the amines are protonated. The polymer is depicted in the hydrochloride form; a small amount of the halides are bromide. Colesevelam hydrochloride is hydrophilic and insoluble in water.

Reference is made to DMF (b) (4) (by (b) (4)) for all CMC information on the drug substance. The DMF is currently adequate.

- The DMF holder is the drug substance manufacturer of the applicant's approved referenced NDAs. This DMF is not part of these NDAs. The applicant confirmed that there is no difference in the drug substance information of DMF (b) (4) and that of the NDAs.

Drug Product

The drug product is a chewable bar (with input from OPPQ) containing 3.75 g of colesevelam hydrochloride, formulated with food ingredients, and packaged in a child-resistant foil laminate pouch. The bar is 0.33-0.44 in. thick, 3.44-4.13 in. long, and 0.89-1.13 in. wide, and it weighs 28.5-32.5 g.

The food excipients have adequate quality information, and all are confirmed to be well known food ingredients with no safety concern (input from the Pharmacology Toxicology team).

Item	Chocolate Bar	Strawberry Bar	Caramel Bar
Description (Appearance)	Brown, Oblong, rectangular	Pink Oblong, rectangular	Tan Oblong, rectangular
Dosage Form	Chewable bar	Chewable bar	Chewable bar
Picture			
Weight	30 g	30 g	30 g

Inactive ingredients (chocolate): maltitol syrup, maltodextrin, palm oil, glycerin, lecithin, vanilla flavor, rosemary extract flavor, sucralose, alkalized cocoa powder, chocolate flavor.

Inactive ingredients (strawberry): maltitol syrup, maltodextrin, palm oil, glycerin, lecithin, vanilla flavor, rosemary extract flavor, sucralose, gum acacia, FD&C #40 powder, citric acid, strawberry cheesecake flavor.

Inactive ingredients (caramel): maltitol syrup, maltodextrin, palm oil, glycerin, lecithin, vanilla flavor, rosemary extract flavor, sucralose, gum acacia, caramel color, caramel flavor.

Clinically relevant studies submitted in support of the product include an in vitro bioequivalence study with Welchol Tablets and a study of the effects of chewing and digestion on bile acid capacity (reference is made to the Clinical Pharmacology review). The biobatches are also primary stability batches (chocolate 125.6034R3A, strawberry 126.6039R1A, and caramel 127.6032R1A). They were manufactured at the commercial site ((b) (4) at pilot scale ((b) (4) kg).

The drug product manufacturing process consists of (b) (4)

The regulatory drug product specification is adequate based on prior knowledge from the referenced approved NDA 22362 for identification, bile acid binding capacity, assay, and degradants. Content uniformity is a critical quality attribute with USP <905> requirements.

Hardness is a critical quality attribute, with the acceptance criteria of (b) (4) (b) (4) kp; this range is well below the maximum limit of (b) (4) kp for a chewable (b) (4) (as per FDA's current draft guidelines).

There is no dissolution testing because the product is insoluble and does not undergo in vivo absorption.

There is no disintegration testing because the product must be chewed by the patient. Clinical data show that chewing the bar for less than 45 seconds resulted in a chewed mass that disintegrated in 5-45 minutes in simulated stomach acid media. The disintegration time of up to 45 minutes reflects the in vivo residence time of the chewed mass (input from the Clinical team).

Microbial limits are adequate with the addition of bile tolerant gram-negative bacteria testing in the drug product specification (see Chapter VIII of this review for details). *[Note: Information on the Enterobacteriaceae and gram-positive cocci contamination is being handled as GMP issues,covered by the Facilities inspection of the drug product manufacturing site.]*

Primary container closure system: Child-resistant white foil laminate (b) (4) wrapper (input from DMEPA on the child-resistant information).

Expiration Date & Storage Conditions: *To be determined in the next review cycle*
The following will be included in the CR letter (not an approvability deficiency): "In the resubmission, provide 24-month stability data for the six registration batches (b) (4) kg) and all available stability data for the six demonstration batches (b) (4) kg)." *[Note: The comment is revised from the original comment in Chapter II to add clarity, with supervisory concurrence.]*

B. Special Product Quality Labeling Recommendation: not applicable

C. Life Cycle Knowledge Information/ Final Risk Assessment:

API	none
Drug product	none
Process	page 2 of Chapter V
Facilities	page 6 of Chapter VI
Microbiology	none

Application Technical Lead Signature:
I concur with the reviewers' recommendations.

Suong T. Tran -S

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Date: 2018.05.17 13:02:20 -04'00'

Suong (Su) Tran, Ph.D.
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CHAPTERS: Primary Quality Assessment

Chapter I: Drug Substance
Chaper II: Drug Product
Chapter III: Environmental Assessment
Chapter IV: Labeling
Chapter V: Process
Chapter VI: Facilities
Chapter VII: Biopharmaceutics (not applicable)
Chapter VIII: Microbiology
Attachment I: Final Risk Assessment (see last page of Executive Summary)

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Anne Russell

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Danae Christodoulou

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CHAPTER III: Environmental Analysis

ENVIRONMENTAL

R Regional Information

Background

Application: NDA 210895

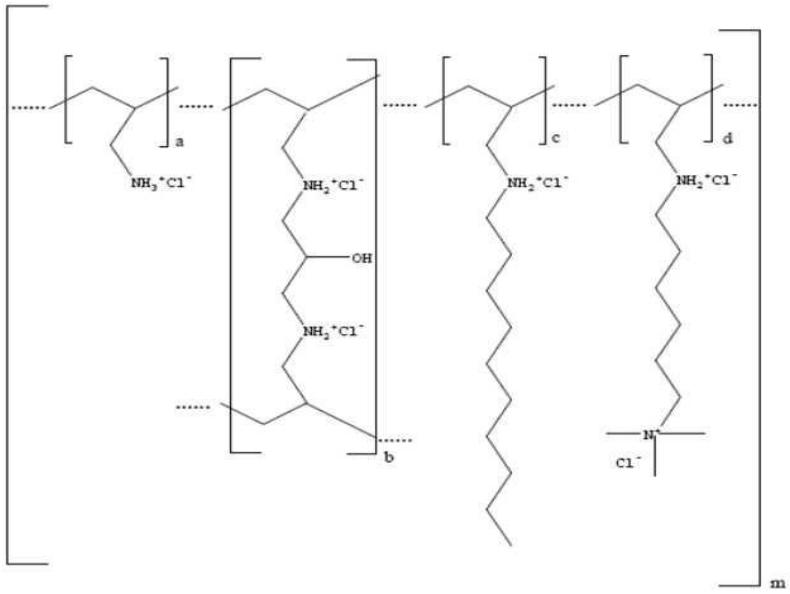
Applicant: Daiichi Sankyo Inc.

API: Welchol® (colesevelam hydrochloride) Chewable Bar
Indication: Welchol® is a bile acid sequestrate indicated as an adjunct to diet and exercise to: • reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia as monotherapy or in combination with a hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor (statin); • reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia as monotherapy or in combination with a statin after failing an adequate trial of diet therapy and •improve glycemic control in adults with type 2 diabetes mellitus.

The applicant has submitted an updated Environmental Assessment (EA) dated September 1, 2017. Previous EAs for Welchol® have been submitted for capsules (NDAs 21-141), tablets (NDA 21-176) and oral suspension forms (NDA 22-362). Findings of No Significant Impact were prepared for the previous EAs based on exposure/toxicity considerations and the physical/chemical nature of colesevelam hydrochloride. The present EA is an update to the environmental assessment filed in the initial NDA 22-362 application. Refer to the previous EAs and reviews for additional information. This review will focus on the critical revisions to the previously submitted EAs.

Colesevelam hydrochloride is a highly cross-linked polymer that is insoluble in aqueous and organic solvents. Due to this insoluble nature, Colesevelam HCL is expected to settle out into biosolids in waste water treatment systems. Land application of biosolids creates an exposure pathway to terrestrial organisms. The EA evaluates potential risks to terrestrial receptors (e.g., soil microorganisms, land plants, and soil invertebrates) in addition to aquatic receptors.

Colesevelam HCL Structure



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

Physical/Chemical Characteristics/Depletion Mechanisms/Environmental Effects

(b) (4)

Environmental Review

Aquatic and Terrestrial Exposure Concentrations

Of note in the revised EA is the significantly lower projected sale volume of colesevelam HCl. This corresponds to significantly lower aquatic expected introductory concentrations (EIC) and soil expected environmental concentrations than provided in the previous EAs

The EA provides the following discussion of projected sales from 2018 through 2022:

The current colesevelam HCl forecast (through 2022) of (b) (4) metric tons/yr is significantly lower than that previously projected for year 2010 through 2014 (NDA 22-362). The maximum projection for these years ranged from (b) (4) metric tons/yr. The present projection is based on all formulations of Welchol®.

A Five-Year USA forecast for Colesevelam HCl is provided:

Year	Metric
2018	(b) (4)
2019	
2020	
2021	
2022	

The revised aquatic EIC = (b) (4) µg/L as compared to (b) (4) µg/L for 2010 to 2014.

The revised soil EEC = (b) (4) mg/kg as compared to (b) (4) mg/kg for 2010 to 2014.

Toxicity Profile

The toxicity profile of colesevelam HCl is derived from using the most sensitive aquatic and terrestrial species, and comparing to expected maximum environmental concentrations. Hazard ratios in the aquatic and terrestrial compartments is provided as the EC_{50}-LC_{50}/MEEC (maximum expected environmental Concentration; MEEC: EIC or EEC, whichever is greater).

Parameter	Aquatic Environment	Terrestrial Environment
Lowest observed EC_{50}-LC_{50}	(b) (4)	
Maximum Expected Environmental Concentration (MEEC)		
Hazard Quotient (EC_{50}-LC_{50}/MEEC)		

The toxicity value derived for the most sensitive aquatic species is an EC_{50} of (b) (4) mg/L (algal growth 72hr). This was compared to the MEEC of colesevelam HCl in the aquatic environment, which was calculated as discussed above.

The lowest toxicity value derived from the terrestrial studies (i.e., (b) (4) mg/kg dw), was compared to the MEEC of colesevelam HCl in soil.

The lowest observed colesevelam HCl EC_{50} or LC_{50} for acute aquatic toxicity testing (fish, aquatic invertebrate, alga) is more than (b) (4) times greater than the aquatic MEEC.

The lowest observed colesevelam hydrochloride EC_{50} or LC_{50} for acute terrestrial toxicity testing (earthworm, plants) is more than (b) (4) times greater than the soil $MEEC_{soil}$.

These high quotients for aquatic (b) (4)) and terrestrial (b) (4) receptors indicate low risk of significant environmental impacts from the use and disposal of Welchol®.

Literature Search

A literature search did not show a significant risk for colesevelam HCl in the aquatic or terrestrial environment.

Reviewer's Assessment: Adequate

The applicant has submitted an updated Environmental Assessment (EA) dated September 1, 2017. Previous EAs have been submitted for capsules (NDA 21-141), tablets (NDA 21-176) and oral suspension forms (NDA 22-362). Findings of No Significant Impact were prepared for the previous EAs based on exposure/toxicity considerations and the physical/chemical nature of colesevelam HCl. The present EA is an update to the EA filed with NDA 22-362. Of note is the significantly lower aquatic and terrestrial exposure concentrations based on lower projected sales of colesevelam HCl. Comparisons are made to toxicity values for aquatic and terrestrial receptors. These lower exposure concentrations increase the hazard ratio, such that the environmental risk from introduction of colesevelam HCl into the environment from patient use and disposal is reduced as compared to previous estimates. The high hazard

quotients for aquatic ((b) (4)) and terrestrial (b) (4)) receptors indicate low risk of significant environmental impacts from approval of this application.

Based on an evaluation of the information provided in this EA and previous EAs and on FDA Guidance, no significant adverse environmental impacts are expected from the approval of this application.

A Finding of No Significant Impact (FONSI) is recommended for this application.

Primary Environmental Reviewer: Raanan A. Bloom, Ph.D.

Secondary Reviewer: Scott Furness, Ph.D.

Raanan Bloom

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Michael Furness

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Finding of No Significant Impact

NDA 210895

Welchol® (colesevelam hydrochloride) Chewable Bar

Food and Drug Administration
Center for Drug Evaluation and Research

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of the regulatory process.

NDA 210895 requests the approval of Welchol® (colesevelam hydrochloride) Chewable Bar. Each bar containing 3.75 g colesevelam hydrochloride. In support of the application, Daiichi Sankyo Inc. has submitted an environmental assessment (EA; dated September 1, 2017; attached) in accordance with 21 CFR Part 25, which evaluates potential environmental impacts of the approval of this application. The EA characterizes aquatic and terrestrial exposure scenarios and receptors. A hazard quotient analysis is used to compare estimated exposure concentrations to toxicity profiles. Worst case assumptions are used. High quotients for aquatic (b) (4)) and terrestrial (b) (4)) receptors indicate low risk of significant environmental impacts from the use and disposal of Welchol®.

The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and has carefully considered the potential environmental impact due to approval of this application. Based on review of this information and information in the original applications, FDA has determined that approval of the application is not expected to have a significant impact on the human environment. Refer to the EA for supporting information. Therefore, FDA is issuing a finding of no significant impact (FONSI), and an environmental impact statement will not be prepared.

Raanan Bloom

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Michael Furness

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CHAPTER VII: Biopharmaceutics

Not applicable

CHAPTER VIII: Microbiology

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

DATE: 04/12/2018

TO: Anika Lalmansingh
Regulatory Health Project Manager, CDER
OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI

FROM: Koushik Paul
Review Microbiologist
CDER/OPQ/OPF/DMA/Branch 1
(240) 402-2193

THROUGH: Erika Pfeiler
Acting Quality Assessment Lead
CDER/OPQ/OPF/DMA/Branch 1

SUBJECT: *NDA*: 210895
Submission Date: 10/30/2017, and 04/06/2018
Receiving Date: 10/30/2017, and 04/06/2018
Drug Product: Welchol (Colesevelam Hydrochloride)
Applicant: Daiichi Sankyo, Inc.
Manufacturer: (b) (4)

Daiichi Sankyo submitted an NDA for nonsterile drug product [WELCHOL® (colesevelam hydrochloride) chewable bar]. WELCHOL® is being developed to reduce elevated low-density lipoprotein cholesterol in adults and children ages 10-17 years, and also to improve glycemic control in adults with type 2 diabetes mellitus. The DMA does not generally perform product quality microbiology review for non-sterile solid oral dosages; however, upon request from the drug product and process reviewer, the following microbiology consult is conducted.

The drug product and process reviewer were concerned about the presence of *Enterobacteriaceae and* Gram-positive cocci in the exhibit batch (data can be found in 3.2.P.5.4 Control of Drug Product - *Batch Analyses.pdf, submission date 10/30/2017*). The microbial testing is performed as per USP <61> and USP <62> [analytical procedure/SOP # M13150], which includes testing for the Total Aerobic Microbial Count (TAMC), Total Yeast and Mold Count (TYMC) and *Escherichia coli.* The data is provided for 18 exhibit batches. Only the summery of batch data contaminated with *Enterobacteriaceae and* Gram-positive cocci are captured below:

Microbial Limits testing	
Test parameters	Microbial Limits testing is performed as per USP<61> and USP<62>) [analytical procedure/SOP # M13150]

M E M O R A N D U M

Acceptance Criteria	**TAMC:** (b) (4) **TYMC:** ***E. coli*:**
Batch Results	
DSIW-125.7191-DB1	Complies; however, contaminated with *Enterobacteriaceae* and *Enterobacter hormaechei steigerwaltii*.
DSIW-125.7191-DB2	Complies; however, contaminated with *Enterobacter hormaechei steigerwaltii*.
DSIW-127.6032R1A	Complies; however, contaminated with Gram-positive cocci.
DSIW-127.7194DB1	Complies; however, contaminated with *Enterobacter hormaechei steigerwaltii*.
DSIW-127.7194DB2	Complies; however, contaminated with *Enterobacteriaceae* and *Enterobacter hormaechei steigerwaltii*.

Note to Reviewer: Please note that before the manufacturing facility inspection, we had a meeting with FDA investigators and various other disciplines on 03/05/2018. We have discussed and raised our concern regarding the *Enterobacteriaceae* contamination in the finished drug product. The following deficiencies were also conveyed to the applicant.

03/08/2018 Information Request: *It is acknowledged that based on the USP <1111> the applicant has performed an adequate microbial test for the subject drug product. However, the presence of Enterobacteriaceae could demonstrate a lack of control in the manufacturing process and could also present a risk for the patient. Therefore, under these circumstances following information is requested prior to the approval of an NDA:*

a. Please describe the Enterobacteriaceae contamination source and control strategy for the subject drug product. Additionally, please clarify the significance of this contamination and indicate the outcome of any investigations that resulted from this identified contamination.

04/06/2018 Response: The applicant states that they are currently conducting investigations to identify *Enterobacteriaceae* contamination source for all contaminated batches. During the investigation, *Enterobacteriaceae* was identified on (b) (4), and therefore they have concluded that the potential sources for the contamination are (b) (4)

b. Please comment what future steps will be taken to prevent this contamination from occurring. In addition, we encourage you to consider adding a release specification for Bile Tolerant Gram-Negative bacteria (please consult USP <62> for methods and suitability studies).

04/06/2018 Response: Based on the investigation into the contamination events, the applicant will implement an (b) (4) procedure for the manufacturing of Welchol Chewable Bars. The following preventative actions will be taken in future, which includes but not limited to:

M E M O R A N D U M

- (b) (4)
- Include Bile Tolerant Gram-Negative bacteria testing (as per USP <62>) in the release specification of the drug product.

Note to reviewer: The applicant's proposed cleaning strategy will serve to mitigate the risk of contamination of the product with *Enterobacteriaecae*. The applicant also proposes to implement testing for bile-tolerant Gram-negative organisms, following completion of suitability testing. Since this testing is not included in the testing recommendations provided in <1111> (and the applicant is performing testing as described in <1111>, no further information will be requested from the applicant regarding this implementation.

Remarks: The submission is **recommended** for approval.

Reviewers:

Microbiologist/Koushik Paul, Ph.D.

Microbiology secondary reviewer/ Erika Pfeiler, Ph.D.

Koushik Paul

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Erika Pfeiler

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ATTACHMENT I: Final Risk Assessments

See Executive Summary

Su (Suong) Tran

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