

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210895Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 48034

MEETING MINUTES

Daiichi Sankyo Inc.
Attention: Scott Greenfeder, PhD
Senior Director, Regulatory Affairs
211 Mount Airy Road
Basking Ridge, NJ 07920-2311

Dear Dr. Greenfeder:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Welchol (colesevelam) tablets.

We also refer to the telecon between representatives of your firm and the FDA on July 24, 2017. The purpose of the meeting was to discuss your plans to submit a marketing application for a chewable (b) (4) formulation.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kati Johnson, Senior Regulatory Project Manager at 301-796-1234.

Sincerely,

{See appended electronic signature page}

James P. Smith, MD, MS
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Teleconference Date and Time: July 24, 2017, 2 pm
Teleconference Number: (b) (4)
Conference code= (b) (4)

Application Number: IND 48034
Product Name: Welchol (colesevelam) tablets
Indication: WELCHOL is a bile acid sequestrant 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 an 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.
- improve glycemic control in adults with type 2 diabetes mellitus

Sponsor/Applicant Name: Daiichi Sankyo

Meeting Chair: James P. Smith, MD, MS
Meeting Recorder: Kati Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products (DMEP)

James P. Smith, MD, MS-Deputy Director
Ovidiu Galescu, MD-Clinical Reviewer
Kati Johnson-Senior Regulatory Project Manager

Office of Clinical Pharmacology (OCP), Div. of Clinical Pharmacology II (DCPII)

Jaya Vaidyanathan, PhD-Clinical Pharmacology Team Leader
Mohammad Absar, PhD-Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ), New Drug Products, Branch VI

Suong Tran, PhD-Quality Assessment Lead

SPONSOR ATTENDEES

Daiichi Sankyo

Name	Title
George Chen, Ph.D	Executive Director, Regulatory Affairs-CMC
Scott Greenfeder, Ph.D	Sr. Director, Regulatory Affairs-Strategy
Linda Nelson, Ph.D	Director, Regulatory Affairs-CMC
Radha Ramkumar	Sr. Director, Project Management
Joan Rogers	Sr. Director, Established Products, DSAC Market Access Strategy
Jack Rosen	Director, CMC Management & Operations

(b) (4)

(b) (4)	Vice President, Formulation Development
(b) (4)	Vice President, Operations

1.0 BACKGROUND

Welchol was approved May 26, 2000, as monotherapy or in combination with statins for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia (Fredrickson Type IIa). Although it was approved as both tablets (NDA 21176) and capsules (NDA 21141), on the same day, the capsule formulation has never been marketed.

Welchol for Oral Suspension was approved October 2, 2009 (NDA 22362), after demonstrating in vitro bioequivalence with the tablet formulation. The tablet and oral suspension formulations share a common package insert.

The firm is now developing a chewable (b) (4) formulation and has requested a pre-NDA meeting. (b) (4) assisted Daiichi Sankyo in developing the formulation and will manufacture the product following approval.

Preliminary Comments were sent to Daiichi Sankyo on July 20, 2017.

Prior to the telecon, the firm submitted a document titled "Daiichi-Sankyo Request for Clarification of FDA Meeting Preliminary Comments" which is attached to these telecon minutes.

2. DISCUSSION

The firm's questions and background information are in regular text. Preliminary responses are in **bolded** text. Meeting discussion is in *italicized* text. Post-meeting comments are in **bolded underlined** text.

Question 1

The NDA for Welchol Chewable Bar will be submitted in electronic CTD format and the major contents are listed below:

- cross-reference to the approved Welchol NDAs (21141, 21176, and 22362) with subsequent supplements and Annual Reports for all nonclinical, clinical, and clinical pharmacology information,
- cross-reference to drug substance drug master file (DMF) for drug substance CMC information,
- complete drug product CMC information in the NDA (3.2.P),
- *in vitro* BE study, full pharmaceutical information, and documentation on the Welchol Chewable Bar drug product in the NDA,
- patent certification,
- pediatric waiver request, and
- no new clinical data.

1a. Does the Agency agree that the proposed content and format of the new NDA for Welchol Chewable Bar would be sufficient and adequate to support registration?

1b. Does the Agency agree that no clinical data would be required for the new NDA for Welchol Chewable Bar?

Background

All nonclinical, clinical and clinical pharmacology information is provided in the approved Welchol NDAs (21141, 21176 and 22362) and post approval submissions. We plan to have pediatric data for the Welchol for Oral Suspension dosage form from the ongoing pediatric clinical study WEL-A-U307 submitted to the Welchol NDA 22362 end of 2019 in accordance with a Post Marketing Commitment for this NDA.

FDA Response to Question #1:

[From Quality CMC] Your proposal to cross-reference the drug substance DMF is acceptable. In Form 356h of the new NDA, provide the complete list of drug substance manufacturing and testing facilities that will be involved in the manufacture of the new commercial product. We remind you that any excipient that has not been approved by FDA in a drug is considered a novel excipient, and complete CMC information on the material should be provided in the NDA or a referenced DMF.

[From Pharmacology/Toxicology] Provide adequate safety information for those excipients that are not listed in the FDA's inactive ingredient database (IID) (e.g., colorants and flavors) and for those excipients that are noncompendial or are present at higher concentrations than those listed in the IID. Additionally, any impurity or degradant in your drug substance/product that exceeds thresholds per ICH Q3A, ICH Q3B, or ICH M7 should be adequately qualified.

[From Clinical Pharmacology] See responses to Questions 7 and 8.

Meeting Discussion: None

Question 2

The proposed dose and indications for Welchol Chewable Bar are the same as the approved Welchol Tablet and Welchol for Oral Suspension based on BE data. In accordance with the Post Marketing Commitment for Welchol for Oral Suspension, the Sponsor has initiated a pediatric study (WEL-A-U307) under NDA 22362. The study is still ongoing, and the results are expected around the end of 2019. [REDACTED] (b) (4)

Does the Agency agree [REDACTED] (b) (4) in the new NDA for Welchol Chewable Bar would be sufficient to fulfill Pediatric Research Equity Act requirements?

FDA Response to Question #2: See “Other Important Meeting Information” below. Under the Pediatric Research Equity Act all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Your proposal to market a chewable formulation represents a new dosage form. In your initial Pediatric Study Plan, you must address each indication for which you will seek approval for the current product. If you intend to seek waivers and/or deferrals, include your justification in the document.

As a point of clarification, your ongoing pediatric study under NDA 22362 is a post-marketing requirement (PMR 1726-1), established under PREA, not a post-marketing commitment. The final report submission is due November 2019.

Post-meeting comment: Following the meeting, the firm contacted the Agency and asked [REDACTED] (b) (4)

Normally, an iPSP is required to be submitted within 60-days following an end-of-phase 2 meeting, or, in the absence of such meeting (as in this case), 210 days prior to the planned submission of the NDA. Daiichi-Sankyo is proposing to submit the NDA in mid-October 2017.

Following internal discussions with the Pediatric Review Committee (PeRC), the firm was instructed to include an initial Pediatric Study Plan (iPSP) in the NDA and it will be reviewed as part of the application.

Meeting Discussion: None

Question 3

It is the Sponsor’s understanding that an acceptable dosage form nomenclature for the product based on the FDA Dosage Form Monograph (C-DRG-00201) would be Welchol “Chewable Bar”. However, to convey the nature of the commercial product the Sponsor suggests that Welchol [REDACTED] (b) (4) provides a more accurate depiction of the product and distinguishes it more effectively from other chewable products such as gums.

Does the Agency agree with naming the new dosage form as Welchol [REDACTED] (b) (4) ?

FDA Response to Question #3: This is a labeling issue and will be evaluated as part of our review of the NDA; comments will be conveyed to you after our evaluation of all available information in the application. We strongly recommend that you work with USP to add your proposed dosage form to the compendial chapter on pharmaceutical dosage forms; you should include all communications with USP in the NDA for our consideration.

Meeting Discussion: None

Question 4

The Sponsor intends to add Welchol Chewable Bar to the current Welchol package insert, providing a single package insert for all three dosage forms of Welchol, i.e., Welchol Tablet, Welchol for Oral Suspension, and Welchol Chewable Bar.

Does the Agency agree with the Sponsor's intent?

Background

Daiichi Sankyo plans to expand the approved Welchol package insert to incorporate the Welchol Chewable Bar dosage form. This will allow us to have a single package insert for the currently approved Welchol tablet and Welchol for Oral Suspension and for the new chewable bar dosage forms. The following sections of the package insert will require changes:

- Dosage and Administration,
- Dosage Forms and Strengths,
- Description,
- How Supplied/ Storage and Handling,
- Patient Counseling Information.

Throughout the text of the labeling other modifications may be necessary to accommodate the multiple dosage forms.

FDA Response to Question #4: Labeling will be discussed following a comprehensive review of the application.

Meeting Discussion: None

Question 5

[Redacted content] (b) (4)

Background

[Redacted content] (b) (4)

FDA Response to Question #5: No, we do not agree. As per the approval letter of your referenced NDA 21176 S-017, you should submit an updated Environmental Assessment (EA) in the new NDA because colesevelam HCl is an insoluble polymer that is expected to partition to wastewater treatment plant biosolids.

Meeting Discussion: None

Safety

Question 6

Based on the well-established safety profile of Welchol Tablets and Welchol for Oral Suspension along with the demonstrated BE between Welchol Chewable Bar and Welchol Tablets, no specific Risk Evaluation and Mitigation Strategy or other risk minimization activities are planned for Welchol Chewable Bar. A routine pharmacovigilance approach will be applied once Welchol Chewable Bar is marketed.

Does the Agency agree that no specific Risk Evaluation and Mitigation Strategy or other risk minimization activities except routine pharmacovigilance would be required for Welchol Chewable Bar?

Background

Routine pharmacovigilance activities conducted by the Sponsor includes continuous review of adverse reactions received from all sources and periodic cumulative review for identification of potential safety issues and analysis for appropriate world-wide risk minimization activities. Since the US marketing authorization of Welchol Tablets in May 2000 and the Welchol for Oral Suspension in October 2009, review of Welchol related safety information was consistent with the known safety profile from its clinical trials. Pharmacovigilance surveillance in the post marketing period resulted in updating of the prescribing information, patient package insert and package leaflet. There have been no safety concerns identified with Welchol Tablets or Welchol for Oral Suspension above and beyond the prescribing information and information for patients. Based on the well-known safety profile of colesevelam hydrochloride and the Sponsor's routine pharmacovigilance activities which include on-going review of Adverse Drug Reactions received from all sources world-wide with periodic analysis of cumulative safety data and appropriate risk minimization activity, Risk Evaluation and Mitigation Strategy is deemed not needed for the Welchol Chewable Bar drug product.

FDA Response to Question #6: Given the information available at this time, we anticipate that routine pharmacovigilance would be sufficient for this product; however, a final determination regarding whether a REMS would be required is made during the review of the application.

Meeting Discussion: None

Bioequivalence

Question 7

The approach to demonstrating bioequivalence between the commercial Welchol Tablets (used as the reference) and the Welchol Chewable Bar (all three flavors) utilized *in vitro* binding

assays of bile salts as outlined in the FDA's Product Specific Bioequivalence Draft Guidance on Cholestyramine (June 2015). In FDA's Written Response issued December 15, 2015, the proposal for *in vitro* bioequivalence studies appeared acceptable to the Agency. The two types of testing performed were Equilibrium Binding and Kinetics Binding, both of which monitor the binding reaction of the three bile acids: Glycocholic Acid (GC), Glycochenodeoxycholic Acid (GCDC) and Taurodeoxycholic Acid (TDC).

Are the studies that have been provided in this briefing book adequate and sufficient to demonstrate the bioequivalence between the commercial Welchol Tablets (used as the reference) and the Welchol Chewable Bar (all three flavors)?

FDA Response to Question #7:

Your proposal for demonstrating bioequivalence between the commercial Welchol Tablets and the Welchol Chewable Bar appears to be reasonable. The acceptability of the study results will be a review issue. In addition, the study report should address the following comments:

- i. You have provided the 90% confidence interval (CI) values for the T/R ratios of the capacity constant, k_2 , based on total bile salt binding (GC+GCDC+TDC). Provide also the 90% CI values for the T/R ratios of k_2 for individual bile acid binding.**
- ii. Justify the use of 4.75 g of the chewable bar (equivalent to 600 mg of colesevelam) in the *in vitro* kinetic binding study.**
- iii. Submit details of the analytical method and the validation report for the *in vitro* BE studies.**

Meeting Discussion: The Agency agreed that the primary determination of bioequivalence may be based on the total bile salt binding, but comparisons with respect to individual bile salt binding should be provided as supportive data for review.

*Regarding the Agency's comment to justify the use of 4.75 g of the chewable bar (equivalent to 600 mg of colesevelam) in the *in vitro* kinetic binding study, the sponsor was requested to provide the details in the submitted application.*

Question 8

In response to our September 30, 2015 General Correspondence submission to the Division of Metabolism and Endocrinology Products, the FDA commented that we should address whether there is any impact of chewing on *in vivo* performance of the proposed formulation, e.g., alteration of bile acid binding. In response to this request, Daiichi Sankyo completed a study to evaluate the impact of chewing on bile acid binding by reducing the typical bite size of the chewable bar drug product to a size suitable for swallowing and then determining the bile acid binding capacity on various sample sizes. In this study, small, medium and large samples were evaluated to simulate different sizes of chewable bar pieces chewed and swallowed by the patients. The data demonstrate that different sample sizes of chewable bar pieces, simulating various degrees of chewing prior to swallowing, do not impact the bile acid binding of the product.

Does the Agency agree with the conclusion of the study that there is no impact of chewing on in vivo performance of the proposed formulation, e.g., alteration of bile acid binding?

FDA Response to Question #8:

The study performed to assess the impact of chewing on in vivo performance of the proposed formulation using different sizes of the chewable bar pieces does not mimic the chewing condition. Justify in your application how the different sizes of bar simulate the chewing condition, which involves mastication and crushing/grinding by teeth in the presence of salivary enzymes. Further, the binding study was conducted for a period of 4 hours with two bile salts, which is not adequate. It is recommended that you conduct the in vitro equilibrium binding study to assess the impact of chewing on in vivo performance.

Meeting Discussion: The firm reviewed the attached document, which provided their justification for the chewing study and the rationale for the study design.

The Agency agreed that chewing and digestion are complex processes, and the Agency's comments referencing chewing, specifically, perhaps did not adequately convey the concern underlying the request. The dosage form being considered is novel, so the Agency will closely review whether the in vitro assessments will adequately support safety and effectiveness of this product compared with the listed product. For example, when a patient eats the soft bar, they will chew it and form a bolus to swallow. When the product reaches the site of action in the gastrointestinal tract, will it exist in a form that would make the in vitro assessments relevant?

Although the firm stated that there is no commercially available standard equipment to perform a chewing study for a chewable bar product, the Agency stated that this could be circumvented with a clinical trial, which would directly assess the effects of the product when consumed. To date, the Agency has not stated that a clinical trial would be required to file an application, but if the in vitro studies and accompanying justification are not sufficiently persuasive after our review, a trial could become a requirement for approval.

Chemistry, Manufacturing and Controls

Question 9

All of the tests and methods for the Welchol Chewable Bar are consistent with those used for the Welchol Tablets and Welchol for Oral Suspension commercial drug products. Minor modifications of these methods were required to accommodate the physical and compositional differences of the chewable bar drug product versus the two approved Welchol drug products. The Sponsor recognizes that the assessment of specifications is a review issue; our intent is to provide an early understanding of the selection of the proposed test parameters, test methods and acceptance criteria to control and monitor drug product quality and stability as well as available data sets at the time of NDA filing.

Does the Agency agree with our approach for the drug product control strategy as presented?

FDA Response to Question #9: The control strategy will be evaluated as part of our review of the NDA; comments will be conveyed to you after our evaluation of all available

information in the application. The drug product specification should include Hardness, Disintegration, and Dissolution.

Meeting Discussion: Our responses to your questions serve as general guidance to help you prepare your NDA submission. They are not meant to be the starting point of any negotiation. Our decisions on the issues that you raised will be made after our review of the complete NDA and based on all available information at that time, including the information and justification that you provided in the follow-up communication.

Question 10

(b) (4)

The Sponsor proposes

(b) (4)

Agency agree with this approach?

Does the

FDA Response to Question #10: The drug product stability data in the NDA should include at least 12-month long-term data on three primary batches of the same formulation, manufactured by a process simulating the commercial process, and packaged in the commercial container closure systems (see ICH Q1A, current revision). Your proposal to submit (b) (4) during the NDA review cycle is not acceptable. We expect the application to be complete at the time of submission.

Additional comment: Add Disintegration and Dissolution to the stability specification and provide data in the NDA in support of the proposed limits. In addition, propose limits on Hardness, Dosage Unit Mass, and Package Seal Integrity with justification.

Meeting Discussion: The proposed submission of a reduced stability package would not be a filing issue for the NDA submission but it may result in a short expiration dating period, especially in the case of a novel dosage form. In accordance with Good Review Management Principles and Practices (GRMPs) timelines, a complete NDA should be submitted for filing, and we do not commit to reviewing any unsolicited amendment, such as additional stability data, during the review cycle.

Question 11

An observation from the registration stability program was that the strawberry and caramel flavored Welchol Chewable Bars exhibited a change in color for the appearance test when stored at ICH accelerated storage conditions. For example, the color of the strawberry chewable bar goes from pink when stored at 25°C/60%RH to a darker pink when stored at 30°C/65%RH, and then to almost red when stored at 40°C/75%RH. The Sponsor has performed substantial analytical studies to determine the mechanism of the color change and the potential impact on product quality, potency and performance. The Sponsor recognizes that the assessment of this information is a review issue. Our intent here is to provide the Agency with an early understanding of the observation. Our studies have shown that we understand the mechanism of color formation and that there is no impact of the color change on bioequivalence.

Question 11a: Does the Agency agree [REDACTED] (b) (4) [REDACTED] ?

FDA Response to Question #11a: The stability data and related information will be evaluated as part of our review of the NDA; comments will be conveyed to you after our evaluation of all available information in the application.

Meeting Discussion: None

Question 11b: Does the Agency agree that the observed color change [REDACTED] (b) (4) [REDACTED] has no impact on the bioequivalence between Welchol Chewable Bars and Welchol Tablets?

FDA Response to Question #11b: See Response to #11a.

Meeting Discussion: None

Question 11c: Based on the Sponsor's understanding of the mechanism of discoloration and the data from the in-vitro BE study using stability samples that have undergone a color change, the Sponsor proposes that the observed color change [REDACTED] (b) (4) [REDACTED] has no impact on quality, safety and efficacy of the Welchol Chewable Bar drug product. Does the Agency agree?

FDA Response to Question #11c: See Response to #11a. In addition, we remind you that ICH identification and qualification thresholds will apply to all impurities, [REDACTED] (b) (4) [REDACTED] and any other drug- or excipient-related degradant.

Meeting Discussion: None

Question 12

There are three flavors of Welchol Chewable Bar packaged in child-resistant [REDACTED] (b) (4) [REDACTED] laminate foil materials. [REDACTED] (b) (4) [REDACTED]. Given the commonalities in the batch records, we

propose submitting only one executed full scale batch record for each Welchol Chewable Bar flavor.

Daiichi Sankyo proposes to provide a single executed batch record for each flavor manufactured at full scale (demonstration batch) and packaged in the commercial child-resistant packaging configuration. Is this proposal acceptable to the Agency? (b) (4)

Note: All original batch records are documents would be available for Field Staff during a site inspection.

FDA Response to Question 12: Your proposal to include in the NDA one executed batch record for each flavor manufactured at full scale and packaged in the commercial packaging configuration is acceptable for our filing review. Be advised that additional batch records may be requested (i.e., to be submitted to the NDA) during our review of the application.

Meeting Discussion: None

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

"Daiichi-Sankyo Request for Clarification of FDA Meeting Preliminary Comments"

20 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JAMES P SMITH
08/24/2017