

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200175

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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

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

NDA NUMBER

200175

NAME OF APPLICANT/NDA HOLDER

Daiichi Sankyo, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

(b) (4) (proposed)

ACTIVE INGREDIENT(S)

olmesartan medoxomil/amlodipine/hydrochlorothiazide

STRENGTH(S)

20/5/12.5 mg; 40/5/12.5 mg; 40/5/25 mg; 40/10/12.5; and
40/10/25 mg

DOSAGE FORM

Tablet

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

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

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

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

1. GENERAL

a. United States Patent Number

5,616,599

b. Issue Date of Patent

4/1/1997

c. Expiration Date of Patent

4/25/2016

d. Name of Patent Owner

Daiichi Sankyo Company, Limited

Address (of Patent Owner)

3-5-1, Nihonbashi Honcho

City/State

Chuo-ku, Tokyo

ZIP Code

103-8426 JAPAN

FAX Number (if available)

011-81-3-5696-8773

Telephone Number

011-81-3-5696-8270

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Arthur Mann, Esq.

Address (of agent or representative named in 1.e.)

Daiichi Sankyo, Inc.

City/State

Parsippany, NJ

ZIP Code

07054

FAX Number (if available)

(973) 944-2808

Telephone Number

(973) 944-2623

E-Mail Address (if available)

amann@dsi.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 26, 27, 33, 38, and 42	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Under the heading INDICATIONS AND USAGE, it states that the drug product "is indicated for the treatment of hypertension."
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5. No Relevant Patents

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

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



8/7/09

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

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Arthur Mann, Esq.

Address

Daiichi Sankyo, Inc.
2 Hilton Court

City/State

Parsippany, NJ

ZIP Code

07054

Telephone Number

(973) 944-2623

FAX Number (if available)

(973) 944-2808

E-Mail Address (if available)

amann@dsi.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 200175

SUPPL #

HFD #

Trade Name TRIBENZOR

Generic Name olmesartan, amlodipine, HCTZ

Applicant Name Daiichi-Sankyo

Approval Date, If Known 7/23/10

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505b2

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 19787	Norvasc (amlodipine)
NDA# 21286	Benicar (olmesartan)
NDA# 11793	Esidrix (hydrochlorothiazide)

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

CS8635-A

"A randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide in Subjects with Hypertension"

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

CS8635-A

"A randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide in Subjects with Hypertension"

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

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

Investigation #1
IND # 77651 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

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

interest provided substantial support for the study?

Investigation #1
!
! YES NO
! Explain: ! Explain:

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

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

YES NO

If yes, explain:

Name of person completing form: Russell Fortney
Title: Regulatory Project Manager
Date: 7/16/10

Name of Office/Division Director signing form: Norman Stockbridge
Title: Director, Division of Cardiovascular and Renal Products

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

RUSSELL FORTNEY
07/23/2010

NORMAN L STOCKBRIDGE
07/23/2010



Daiichi Sankyo

1.3.3 Debarment

Daiichi Sankyo Pharma Development
CS-8635 Tablets

On behalf of Daiichi Sankyo, Inc., I hereby certify that we did not and will not use in any capacity the services of any individual, partnership, corporation, or associations debarred under sub-sections (a) or (b) of Section 306 of the Federal Food, Drug, & Cosmetic Act in connection with NDA 200175 for the combination of Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide.

Manini Patel

Print Name

*Assoc. Director, Regulatory Affairs
Daiichi Sankyo, Inc.*

Title

M. Patel

Signature

9/15/2009

Date (DD Mmm YYYY)



NDA 0200175

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Daiichi Sankyo, Inc.
399 Thornall Street
Edison, New Jersey 08837

ATTENTION: Manini Patel
Associate Director, Regulatory Affairs

Dear Ms. Patel:

Please refer to your New Drug Application (NDA) dated September 30, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Olmesartan Medoxomil, Amlodipine and Hydrochlorothiazide Tablets, 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, and 40 mg/10 mg/25 mg.

We also refer to your March 30, 2010, correspondence, received March 30, 2010, requesting review of your proposed proprietary name, Tribenzor. We have completed our review of the proposed proprietary name, Tribenzor, and have concluded that it is acceptable.

The proposed proprietary name, Tribenzor, will be re-reviewed 90 days prior to approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 30, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Russell Fortney at 301-796-1068.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

CAROL A HOLQUIST
06/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Russell Fortney, DCRP, 301-796-1068		
DATE 6/7/10	IND NO.	NDA NO. 200175	TYPE OF DOCUMENT Labeling for new NDA	DATE OF DOCUMENT 6/3/10
NAME OF DRUG Tribenzor (olmesartan/amlodipine/HCTZ)		PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG New combination	DESIRED COMPLETION DATE 6/21/10
NAME OF FIRM: Daiichi Sankyo				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review the PPI for this new NDA. Electronic labeling has been sent to OSE via email.				
SIGNATURE OF REQUESTER: Russell Fortney		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

RUSSELL FORTNEY
06/07/2010



NDA 200175

INFORMATION REQUEST

Daiichi Sankyo, Inc.
Attention: Paulette F. Kosmoski
Executive Director, Regulatory Affairs - CMC
399 Thornall St, 11th Floor
Edison, NJ 08837

Dear Ms. Kosmoski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for combination of olmesartan medoxomil / amlodipine / hydrochlorothiazide Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Based on the dissolution data from the pilot and production batches, the Agency recommends the following dissolution acceptance criteria:
 - Olmesartan medoxomil (OM): Q-value of (b) (4) at 30 minutes (all tablets have achieved (b) (4) dissolution at S1 level)
 - Amlodipine (AML): Q-value of (b) (4) at 30 minutes (all tablets have achieved (b) (4) dissolution at S1 level)
 - Hydrochlorothiazide (HCTZ): Q-value of (b) (4) at 15 minutes (all tablets have achieved (b) (4) dissolution at S1 level)

Provide the revised acceptance criteria sheet.

2. Based on the acceptable BE data for the lowest and the highest strengths and the similarity of the dissolution profiles, the Agency considers that your waiver request is acceptable and a biowaiver is granted for the two intermediate strengths; OM/AML/HCTZ 40/10/12.5 mg and 40/5/25 mg.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

RAMESH K SOOD
06/07/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Russell Fortney, PM Division of Cardiovascular and Renal Products 301-796-1068
------------------------------	--

REQUEST DATE 4/22/10	IND NO.	NDA/BLA NO. 200175	TYPE OF DOCUMENTS New NDA Labeling (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Oltmesartan/Amlodipine/HCTZ	PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG New Combination	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 5/31/10
--	------------------------------------	--	--

NAME OF FIRM: Daiichi-Sankyo	PDUFA Date: 7/30/10
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TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
--	--	--

EDR link to submission: <\\CDSESUB1\EVSPROD\NDA200175\200175.ENX>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Substantially complete labeling should be available by the first week in May. When available it will be forwarded to the DDMAC reviewer. No labeling meetings are currently scheduled...we will try to complete our labeling revisions electronically.

SIGNATURE OF REQUESTER: Russell Forteny	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL/DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

RUSSELL FORTNEY
04/22/2010



NDA 0200175

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Daiichi Sankyo, Inc.
399 Thornall Street
Edison, New Jersey 08837

ATTENTION: Manini Patel
Associate Director, Regulatory Affairs

Dear Ms. Patel:

Please refer to your New Drug Application (NDA) dated September 30, 2009, received September 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide Tablets, 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, and 40 mg/10 mg/25 mg.

We acknowledge receipt of your March 22, 2010 correspondence, on March 22, 2010, notifying us that you are withdrawing your February 12, 2010 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of March 22, 2010.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Russell Fortney at 301-796-1068.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

CAROL A HOLQUIST
03/29/2010



NDA 200175

INFORMATION REQUEST

Daiichi Sankyo, Inc.
Attention: Paulette F. Kosmoski
Executive Director, Regulatory Affairs - CMC
399 Thornall St, 11th Floor
Edison, NJ 08837

Dear Ms. Kosmoski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for combination of olmesartan medoxomil / amiodipine / hydrochlorothiazide Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. P.2.2.1 Formulation Development:

Provide details of the experimental design and statistical analysis you employed on the 40/10/25 mg strength tablets in investigating the concentration of the (b) (4) pregelatinized starch and croscarmellose sodium. The details should include the polynomial model used, the regression coefficients for main and interacting independent variables, the standard error, the statistical method to determine significance [statistical criteria for goodness of fit of model (R^2) and p- and t-values to determine the significance of the regression coefficients].

2. P.5.1 Specification

- a. Provide a single consolidated drug product specification table that includes release and stability limits.
- b. Regarding the Degradation Products test in your specification, the unspecified peak amount is attributed to which drug substance? Additionally, provide a justification for the high acceptance criterion of unidentified total on stability (NMT (b) (4)), considering that actual levels on stability are (b) (4).
- c. Regarding the microbial contamination test, you state in P.5.6, 'Justification of Specification' that the frequency of release testing is consistent with the principles of the Periodic Quality Indicator Test (PQIT) program.

Accordingly, this test should not be a part of the drug product specification but as a separate “PQIT” test.

3. P.8.2 Postapproval Stability Protocol and Stability Commitment

Your (b) (4) is not acceptable, (b) (4) Accordingly, each stability batch in your plan should conform to the testing frequency stated in ICH Q1A(R2) 2.2.6. – “- the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period”. Further, the test for microbial contamination should also be performed at the 12 month time point.

4. Review of Common Technical Document-Quality (Ctd-Q) Module

1A. Labeling& Package Insert

The established names on the container label should be in parenthesis, with the word ‘tablets’ inserted after the parenthesis.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

KASTURI SRINIVASACHAR
03/26/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

IND 077651

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Daiichi Sankyo, Inc.
399 Thornall Street, 11th Floor
Edison, New Jersey 08837

ATTENTION: Manini Patel
Associate Director, Regulatory Affairs

Dear Ms. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide Tablets, 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, and 40 mg/10 mg/25 mg.

We also refer to your July 29, 2009, correspondence, received July 30, 2009, requesting review of your proposed proprietary name, (b) (4), and to the amendment dated December 23, 2009 received December 24, 2009. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

d.

(b) (4)



We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Russell Fortney at 301-796-1068.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77651	ORIG-1	DAIICHI SANKYO INC	CS8635 TABLETS

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/s/

DENISE P TOYER on behalf of CAROL A HOLQUIST
01/26/2010



RECEIVED

DEC 24 2009

CDER CDR

DAIICHI SANKYO PHARMA DEVELOPMENT
a division of DAIICHI SANKYO, INC.

399 Thornall Street, Edison, NJ 08837
Tel. 732 590 5000, Fax 732 906 5690

December 23, 2009

Rem #

Dr. Denise Toyer, Pharm.D., Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Road
Beltsville, MD 20705-1266

IND 77,651
**Olmesartan medoxomil/
amlodipine/
hydrochlorothiazide**
(b) (4)
Serial No. 0069

Re: AMENDMENT TO THE PROPRIETARY NAME REVIEW

COPY
TD
74

Dear Dr. Toyer:

Reference is made to the request for proprietary name review ((b) (4)) submitted on July 29, 2009 under our IND 77, 651 as Serial no. 059. Daiichi Sankyo has withdrawn the amendment from NDA 200175 submitted on December 16, 2009 based on the request received from Phuong (Nina) Ton (Safety Regulatory Project Manager) on December 22, 2009 and is submitting this amendment to the IND 77,651.

Additional reference is made to the teleconference between representatives of DMEPA/OSE and Daiichi Sankyo on December 2, 2009, to discuss the proposed proprietary name of (b) (4). During the teleconference DMEPA indicated they had objections with the use of (b) (4) as a proprietary name as a result of their evaluation which included a Google search that identified a similar sound-alike, look-alike product - (b) (4).

[REDACTED]

(b) (4)



Amendment to the proprietary name review

[Redacted text block]

(b) (4)

[Redacted text block]

[Redacted text block]

Product characteristics	
Nonproprietary name	Olmesartan medoxomil/amlodipine/hydrochlorothiazide
Indication	Treatment of hypertension. This fixed dose combination drug is not indicated for the initial therapy of hypertension.
Dosage Form	Tablets
Dosage Strength	Olmesartan medoxomil/amlodipine/hydrochlorothiazide: 20/5/12.5mg 40/5/12.5mg 40/5/25mg 40/10/12.5mg 40/10/25mg
Frequency of administration	Once daily
Route	Oral
Usual Dose	20/5/12.5mg, 40/5/12.5mg, 40/5/25mg, 40/10/12.5mg, or 40/10/25mg per day
Class type (RX/OTC)	Rx
Strength type	Multiple

(b) (4)



Amendment to the proprietary name review

Failure Mode and Effects Analysis (FMEA) was also conducted to assess for the potential for confusion between [REDACTED] ^{(b) (4)} as follows:

FMEA 1:

[REDACTED] ^{(b) (4)}

FMEA 2:

[REDACTED] ^{(b) (4)}

[REDACTED] ^{(b) (4)}

The Agency's November 2008 Draft Guidance (Contents of a Complete Submission for the Evaluation of Proprietary Names) is particularly relevant to the review of [REDACTED] ^{(b) (4)}:

"The overall medication error safety assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. FMEA is used to analyze whether a proposed proprietary name has look- or sound-alike similarities to the names of existing products that could cause confusion and subsequently lead to medication errors in the clinical setting.

To fully assess the safety of proprietary names, it is essential that certain *product characteristics* be considered in the overall risk assessment. The proprietary name and product characteristics provide the framework for how product variables will interact within the medication-use system and provide the context for the verbal and written communication of the drug name. Product characteristics can act together with the orthographic and phonologic attributes of the proprietary name (1) to increase the risk of confusion when there is an overlap in product characteristics among two or more products, or (2) in some instances, to decrease the risk of confusion by helping to differentiate products through dissimilarity. FDA considers product characteristics



Amendment to the proprietary name review

throughout the risk assessment because the product characteristics provide a context for communication of the proprietary name and ultimately determine the use of the product in the usual clinical practice setting. FDA considers typical product characteristics that could lead to confusion with other products, including, but not limited to, the following: • established name of the product • proposed indication • dosage form • route of administration • strength • unit of measure • dosage units • recommended dose • typical quantity or volume • frequency of administration • product packaging • storage conditions • patient population • prescriber population.” (page 5, emphasis in original).”

We recognize that the Agency has emphasized the statement in 21 CFR 201.10(c)(5) that the labeling of a drug may be misleading if “Designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.” However, as noted above, the determination of whether or not similarity in spelling or pronunciation may cause confusion should be made in the context of, and with due consideration of, the respective product characteristics. Consideration of those product characteristics compels the conclusion that there is no risk of confusion between (b) (4) and (b) (4)

In conclusion, Daiichi-Sankyo shares the Agency’s goal of preventing medication errors due to name confusion. In conjunction with the data provided above and the information included in the July 29 submission for (b) (4) proprietary name review, Daiichi Sankyo reasonably concludes that (b) (4) is an appropriate name that can be safely used by healthcare professionals and patients, and that there is no risk of confusion or medication errors between (b) (4) and (b) (4). Based upon these findings, we respectfully request that the Agency reconsider the stated objection and approve (b) (4) as the proprietary name for our combination formulation of olmesartan medoxomil, amlodipine, and hydrochlorothiazide tablets.

Please be advised that the material contained in this submission is considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Should you have questions, please contact me by telephone at (732) 590-4319 or by e-mail at mpatel2@dsi.com. In my absence, please contact Rich Cuprys, Executive Director, Regulatory Affairs at (732) 590-4358.

Sincerely,

**James
McCarthy**

Digitally signed by James McCarthy
DN: o=VeriSign, Inc., ou=VeriSign Trust Network,
ou=www.verisign.com/repository/RPA Incorp. by
Ref.,LIAB.LTD(c)98, ou=Persona Not Validated,
ou=Digital ID Class 1 - Microsoft Full Service,
cn=James McCarthy, email=jmccarthy@dsi.com
Date: 2009.12.23 10:00:12 -05'00'

Manini Patel
Associate Director, Regulatory Affairs

cc: Phuong (Nina) Ton, Pharm.D. Safety Regulatory Project Manager
Sean Bradley, Safety Regulatory Project Manager, Team Leader

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77651	ORIG-1	DAIICHI SANKYO INC	CS8635 TABLETS

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/s/

LAURA L PINCOCK

01/26/2010

Document re-entered into DARRTS on 1/26/10 due to wrong document attached as Appendix J.
The outcome of the review has not changed.

DENISE P TOYER

01/26/2010



NDA 200175

FILING COMMUNICATION

Daiichi Sankyo, Inc.
Attention: Manini Patel
Associate Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Ms. Patel:

Please refer to your new drug application (NDA) dated September 30, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (olmesartan medoxomil / amlodipine / hydrochlorothiazide) Tablets.

We also refer to your submissions dated October 9 and November 17, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is July 30, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 30, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

NORMAN L STOCKBRIDGE
12/10/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **Patrick Marroum, Biopharmaceutics, ONDQA**

FROM (Name, Office/Division, and Phone Number of Requestor):
Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of Kasturi Srinivasachar/Prafull Shiromani

DATE
11/6/2009

IND NO.

NDA NO.
200175

TYPE OF DOCUMENT
original submission

DATE OF DOCUMENT
September 30, 2009

NAME OF DRUG
olmesartan medoxomil/
amlodipine/
hydrochlorothiazide

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
cardio-renal

DESIRED COMPLETION DATE
April 1, 2010

NAME OF FIRM: **Daiichi Sankyo, Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input checked="" type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input checked="" type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input checked="" type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: A review of the dissolution data/method is requested to determine acceptability. The sponsor has requested a biowaiver of the intermediate strengths. A review of this information is also requested.

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

DON L HENRY
11/06/2009

KASTURI SRINIVASACHAR
11/09/2009

REQUEST FOR CONSULTATION

TO (Office/Division): Raanan Bloom, OPS/PARS, (301)796-2185

FROM (Name, Office/Division, and Phone Number of Requestor):
Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of Kasturi Srinivasachar/Prafull Shiromani

DATE
11/6/2009

IND NO.

NDA NO.
200175

TYPE OF DOCUMENT
original submission

DATE OF DOCUMENT
September 30, 2009

NAME OF DRUG
olmesartan medoxomil/
amlodipine/
hydrochlorothiazide

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
cardio-renal

DESIRED COMPLETION DATE
April 1, 2010

NAME OF FIRM: Daiichi Sankyo, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input checked="" type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The applicant claims categorical exclusion from preparation of an environmental assessment. A review of the rationale (calculation) in their comprehensive report is requested.

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

DON L HENRY
11/06/2009

KASTURI SRINIVASACHAR
11/09/2009



NDA 200175

NDA ACKNOWLEDGMENT

Daiichi Sankyo, Inc.
Attention: Manini Patel
Associate Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Mr. Patel:

We have received your new drug application (NDA) submitted section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (proposed) Combination of olmesartan medoxomil /
amiodipine / hydrochlorothiazide) Tablets

Date of Application: September 30, 2009

Date of Receipt: September 30, 2009

Our Reference Number: NDA 200175

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 29, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Mr. Russell Fortney, R.Ph.
Regulatory Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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/s/

EDWARD J FROMM
10/09/2009

Preliminary Responses

Application: IND 77,651
Drug: CS-8635 (olmesartan, amlodipine, hydrochlorothiazide) Tablets
Sponsor: Daiichi Sankyo Pharma Development
Purpose of Meeting: Pre-NDA Meeting
Date of Internal Meeting: July 7, 2009
Date of Meeting with Sponsor: July 16, 2009

List of Internal Meeting Participants:

Thomas Marciniak, M.D.	Medical Team Leader
Divya Menon-Andersen, Ph.D.	Clinical Pharmacology
Charles Resnick, Ph.D.	Pharmacology Team Leader
Fanhui Kong, Ph.D.	Statistician
Edward Fromm	Chief, Project Management Staff
Russell Fortney	Regulatory Project Manager

The following questions were addressed:

1. Adequacy of Non-Clinical Program

During the July 24, 2007 Type C Guidance Meeting, the Agency agreed to the Daiichi Sankyo proposal to conduct one non-clinical study, a 3-month repeated dose toxicity study in rats to evaluate synergistic toxic effects of the combination drug product (olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide) relative to the individual components. Daiichi Sankyo submitted the protocol on July 21, 2008 (serial No. 016) for Agency review and obtained agreement for the protocol execution and the Agency further concurred on September 15, 2008 to a request from Daiichi Sankyo not to require new mechanistic studies for CS-8635.

Daiichi Sankyo proposes to submit the results from the 3-month repeated dose toxicity study and to also cross-reference all non-clinical information from NDA 21-286 for Benicar® (olmesartan medoxomil), NDA 21-532 for Benicar HCT® (olmesartan medoxomil and hydrochlorothiazide), and NDA 22-100 for Azor® (amlodipine besylate and olmesartan medoxomil). Does the Agency agree that the proposed non-clinical information is sufficient for the NDA filing?

Preliminary FDA response: Yes.

2. Adequacy of Clinical Pharmacology Program

2.1 Clinical Pharmacology Program

During the July 24, 2007 Type C Guidance Meeting, the Agency agreed to have additional discussion with Daiichi Sankyo related to the clinical pharmacology program. Daiichi Sankyo submitted the clinical pharmacology development plan (serial No. 009) on January 25, 2008, for Agency review and feedback and obtained agreement on the overall clinical pharmacology program, pending review, to support registration of the triple combination product. Daiichi Sankyo believes that the outlined program is sufficient to support the filing of this NDA for the treatment of hypertension. Does the Agency agree that the proposed clinical pharmacology program is sufficient for filing?

Preliminary FDA response: Yes.

2.2. Modeling and Simulation

The pivotal clinical study did not include an evaluation of the lower dose triple combinations therefore; Daiichi Sankyo had proposed to conduct modeling and simulation in order to obtain information on the lower dose strengths.

During the July 24, 2007 Type C Guidance Meeting, the Agency indicated that the lower dose triple combinations that were not studied could be further supported by CS-8635 Modeling and Simulation (M&S) data. Subsequently, a teleconference was held between the Agency and Daiichi Sankyo on December 17, 2008, the Agency indicated that the Modeling and Simulation was no longer a requirement in order to obtain approval for lower dose strengths as long as the highest dose strength of the triple combination was superior to each of the highest dose strengths of the dual combinations.

Daiichi Sankyo acknowledges the Agency's position on M&S; however we have decided to conduct the M&S to further gain additional information on the blood pressure lowering effects of CS-8635 for the lower triple combination doses not administered in the pivotal clinical study (CS8635-A-U301). Daiichi Sankyo plans to include the M&S data in the NDA, pending a successful validation of the M&S, and proposes to include this information in the Clinical Pharmacology section and other relevant sections such as Dosage and Administration of the proposed label, pending Agency's review. Does the Agency agree with this approach?

Preliminary FDA response: Yes.

3. Adequacy of Clinical Program

3.1. Pivotal Trial

Daiichi Sankyo has completed the double-blind portion (12-weeks) of the proposed pivotal clinical study for CS-8635 entitled "A Randomized, Double-Blind, Parallel Group Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide in Subjects with Hypertension."

During the July 24, 2007 Type C Guidance Meeting, the Agency agreed that one phase III study (CS8635-A-U301) demonstrating that the antihypertensive effect of a triple combination dose (OM, AML, HCTZ) is superior to the dual combination dose (OM/AML, OM/HCTZ and AML/HCTZ) was sufficient, pending review, to support registration of the triple combination product. Daiichi Sankyo believes that this pivotal program is sufficient to support the filing of this NDA for the treatment of hypertension. Does the Agency agree?

Preliminary FDA response: Yes.

3.2 Sub Group Analyses

Daiichi Sankyo proposes to conduct efficacy and safety analyses for the following subgroups: age, gender, hypertension severity, race, diabetic status, body mass index, and renal impairment status. Does the Agency agree that the proposed subgroup analyses are sufficient to support the NDA submission?

Preliminary FDA response: Yes.

4. Subject Exposure in CS-8635 Development Program for Safety Evaluation

During the July 24, 2007 Type C Guidance Meeting, the Agency agreed to the adequacy of the safety program that was presented specific to subject exposure. Daiichi Sankyo believes that the extent and

duration of subject exposure in support of the CS-8635 development program is sufficient for the NDA filing. Does the Agency agree?

Preliminary FDA response: Yes.

5. Adequacy of Special Safety Evaluation

Based on the therapeutic class of the drugs studied, Daiichi Sankyo has specifically evaluated AEs of interest for the combination product. These include edema; hypotension; headache; dizziness and vertigo; syncope; hypokalemia, hyperkalemia; renal-related AEs; hepatic-related AEs; glycemic control; injury, falls and fractures; hyperuricemia, gout, increased uric acid, and the associated MEDRA preferred terms. Daiichi Sankyo considers that this additional safety evaluation, in addition to the standard safety assessments made for these subgroups will adequately characterize the safety profile of the triple combination. Does the Agency agree?

Preliminary FDA response: Yes, with the caveat that safety evaluations must always consider the unexpected.

6. 120-Safety Update Report /40-week Open-label Report

Does the Agency agree with the proposed plan to provide safety data for ongoing and completed studies in the safety update report, and for the 40-week open-label report which will be submitted approximately two months after the 120-day safety update report?

Preliminary FDA response: We agree, however, the 40-week open-label report should be submitted *no later than* 180 days after submission of the application. Please submit a separate SAS data set for the 40-week open label study with initial entry and revisions for adverse events as described in topic 8.5 and case report forms as described in our response to topic 8.6.

7. Risk Evaluations and Mitigation Strategy (REMS)

Based on the safety results obtained from the completed non-clinical and clinical studies in this development program, including the well characterized safety profile of each individual active drug component (olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide), and based upon the belief that restrictions on distribution or administration are not required, Daiichi Sankyo believes that REMS is not required for the NDA and a standard pharmacovigilance approach suffices for monitoring adverse drug reactions for the marketed product. Does the Agency agree that REMS is not required and a standard pharmacovigilance approach suffices for the NDA?

Preliminary FDA response: We agree that it appears at this point that a REMS will not be necessary. However, this decision is subject to change depending on our review of the data.

8. General Topics

8.1 Adequacy of 505(b)(2) Submission

As agreed by the Agency during the July 24, 2007 Type C Guidance Meeting, the proposed NDA will be submitted pursuant to section 505(b)(2). In addition to the results from the completed clinical program, Daiichi Sankyo proposes to cross-reference all clinical information from NDA 21-286 for Benicar[®] (olmesartan medoxomil), NDA 21-532 for Benicar HCT[®] (olmesartan medoxomil and hydrochlorothiazide), and NDA 22-100 for Azor[®] (amlodipine besylate and olmesartan medoxomil). Does the Agency agree with Daiichi Sankyo that this is sufficient for the NDA filing?

Preliminary FDA response: Yes.

8.2 Confirmation of Pediatric Waiver

During the July 24, 2007 Type C Guidance meeting, the Agency agreed to waive the need for evaluation of CS-8635 in the pediatric population. Does the Agency still concur with this position?

Preliminary FDA response: We agree that a waiver for pediatric studies is likely; however, this decision will be reviewed by the Pediatric Review Committee during our review of the application.

8.3 Table of Content (TOC) for Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS)

Daiichi Sankyo will submit CS-8635 in eCTD format. A proposed draft table of contents (TOC) for the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) is provided in Appendix 8 of the briefing package.

Does the Agency agree with Daiichi Sankyo's proposal for the ISE and ISS text portions to be identical to and therefore presented in Modules 2.7.3 and 2.7.4 with appropriate cross-references to Module 5.3.5.3? Does the Agency agree with having the Module 2.7.4 Statistical Analysis Plan (SAP) and supporting tables for the Open-Label integrated analyses and the Phase 1 integrated analyses being placed in Module 5.3.5.3 and the supporting data from stand alone reports in Module 5 in their respective clinical study reports?

Preliminary FDA response: Yes. However, for the ABPM presentations in the ISE, we request graphs of the blood pressure means for each group by post-treatment hour in addition to the 24-hour means.

8.4 Data Structure or Specifications

Daiichi Sankyo plans to submit the datasets in the following format for CS-8635 program:

- For the CS-8635 pivotal study (CS8635-A-U301) and clinical pharmacology studies, the SAS datasets will be provided in CDISC SDTM format (Implementation Guide, version number 3.1.2).
- Safety Evaluation for the CS-866 Phase IV European non-IND study (SP-OLM-03-05) will also be included in the NDA and datasets for this study will be provided in the IVC format (same format as CS-8663 studies previously submitted) and not in CDISC SDTM format, since the clinical study was initiated in 2006.
- Safety Evaluation for the open-label periods of CS-8663 studies (U301 and E303) will also be included in the NDA. Since the datasets and the key results have been previously submitted as part of the Azor[®] sNDA (S-002) for initial therapy Daiichi Sankyo does not plan to re-submit datasets for these two studies (in IVC format) and proposes to cross reference the Azor[®] NDA 22-100; approved on September, 26, 2007.

Does the Agency agree that the proposed dataset structure format is acceptable for the NDA filing?

Preliminary FDA response: Yes.

8.5 Investigator Reported Adverse Event Terms

Daiichi Sankyo utilized Electronic Data Capture (EDC) for the CS8635-A-U301 study. Daiichi Sankyo plans to submit a separate SAS dataset for the electronic case report form (eCRF) Adverse Event Description (investigator reported Adverse Event terms), showing the initial entry and any revisions for each adverse event reported in the original EDC database (InForm[™] version 4.6). Does the Agency agree?

Preliminary FDA response: Yes. Please provide a separate SAS dataset for the 40-week open label study.

8.6 Case Report Forms

For the NDA, Daiichi Sankyo plans to provide the following Case Report Forms (CRFs):

- Deaths, serious adverse events (SAEs) and all discontinuations from the CS-8635 double-blind period of the pivotal study (CS8635-A-U301) and from the six clinical pharmacology studies conducted for the CS-8635 program.
- Deaths, serious adverse events (SAEs) and discontinuations due to adverse events from the supportive CS-866 Phase IV European non-IND study (SP-OLM-03-05).

Since the CRFs for deaths, serious adverse events (SAEs) and discontinuations due to adverse events have been previously submitted for the open-label periods of CS-8663 studies (U301 and E303) as part of the Azor[®] sNDA for initial therapy Daiichi Sankyo (b) (4) proposes to cross reference the Azor[®] NDA 22-100; approved on September 26, 2007.

Does the Agency agree with the proposed submission of CRFs for the NDA?

Preliminary FDA response: Yes. Please provide CRFs for deaths and discontinuations from the 40-week open label study with the 40-week study report. Please also note that CRFs include all clinical information regarding a patient communicated between the investigators and you or your representatives, e.g., CROs., regardless of whether the documents is labeled a CRF. In particular, serious adverse event worksheets or Medwatch type forms are CRFs.

8.7 eCTD format

Daiichi Sankyo intends to submit CS-8635 in eCTD format and the compilation of the eCTD for CS-8635 will be performed by (b) (4) has previously filed an acceptable eCTD pilot with the Agency on June 2, 2004 (pilot no. 900024) and also has previously compiled the eCTD for Azor[®] (NDA 22-100). Accordingly, Daiichi Sankyo requests a waiver of the requirement to provide an eCTD sample submission. Does the Agency agree with our request for a waiver?

Preliminary FDA response: A sample submission is not required.

Signature, Meeting Chair: *{See appended electronic signature page}*
Tom Marciniak, M.D.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 77651

DAIICHI SANKYO INC

CS8635 TABLETS

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/s/

THOMAS A MARCINIAK

07/09/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 77,651

Daiichi Sankyo, Inc.

Attention: Paulette F. Kosmoski, Executive Director, Regulatory Affairs - CMC
399 Thornall St, 11th Floor
Edison, NJ 08837

Dear Ms. Kosmoski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CS-8635.

We also refer to the meeting between representatives of your firm and the FDA on April 3, 2009. The purpose of the meeting was to discuss the overall Chemistry, Manufacturing, and Controls (CMC) development program.

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

If you have any questions, call me at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Don L. Henry
Regulatory Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Daiichi Sankyo, Inc.
Application Number:	IND 77,651
Product Name:	CS-8635 (olmesartan medoxomil & amlodipine besylate & hydrochlorothiazide)
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC), End of Phase 2 meeting
Meeting Date and Time:	Friday, April 3, 2009, 10:00 – 11:00 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	March 3, 2009

FDA ATTENDEES

Office of New Drug Quality Assessment

Christine Moore, Ph.D, Acting Division Director
Kasturi Srinivasachar, Ph.D, Pharmaceutical Assessment Lead
Prfull Shiromani, Ph.D, Review Chemist
Patrick Marroum, Ph.D, Biopharmaceutics Expert
Tapash Ghosh, P.h.D, Biopharmaceutics Reviewer
Don Henry, Regulatory Project Manager

DAIICHI SANKYO INC ATTENDEES

Wolfgang Bauer, Ph.D, Vice Director, Galenical Development
Zoya Borodanski, Associate Director, Regulatory Affairs - CMC
Naoto Fukutsu, Ph.D, Vice Director, Analytical Department
Paulette Kosmoski, Executive Director, US/EU & Regional Regulatory Affairs - CMC
Johann Lichey, Ph.D, Director, Galenical Development
Jun-ichi Okada, Ph.D, Senior Director, CMC Management & Coordination
Andreas Teubner, Ph.D, Vice President, Pharmaceutical Development
Peter Muth, Senior Manager, Analytical Department

1. BACKGROUND

An original Investigational New Drug Application (IND) for CS-8635 was submitted by Daiichi Sankyo, Inc (DSI) on May 1, 2007 (IND 77,651) for treatment of hypertension. On January 27, 2009, Daiichi Sankyo requested a type B End of Phase 2 meeting.

2. DISCUSSION

- 2.1. Briefing Package Question 1: The NDA will provide CMC information for 6 different strengths of the drug product; however, DSI intends to market only 5 strengths. The sixth dose was added to the development program to support international registration. DSI proposes to present information specific to the combination doses intended for commercial distribution for the drug product, the executed batch records, the product labeling and the Environmental Analysis Report. Does the Agency agree with this approach?

FDA Response: *We agree with your proposal. We also recommend that in the NDA submission you identify clearly the strengths for which you are seeking approval and the reason for including the information for the additional strength.*

Meeting Discussion: There was no further discussion on this topic.

- 2.2. Briefing Package Question 2: The particle size distribution (PSD) by laser diffraction for hydrochlorothiazide drug substance consists of (b) (4)

Studies were performed on the influence of the PSD on dissolution performance of the drug product. We believe this examination has justified and substantiated the PSD acceptance criterion for the hydrochlorothiazide drug substance controls or CS-8635 Tablets. As a point of reference information, this PSD acceptance criterion was approved for Benicar HCT[®] Tablets, NDA 21-532. We wish to confirm that the Agency agrees with our assessment approach for certain physical properties characteristics for hydrochlorothiazide drug substance?

FDA Response: *The PSD of all three drug substances will be reviewed to evaluate the impact on dissolution, content uniformity, and the manufacturability of the product. Justification of the proposed acceptance criteria for PSD for each drug substance should be provided in the NDA submission.*

Meeting Discussion: (Slides 5 & 6) The Agency indicated that an evaluation of the particle size typically includes an assessment of the (b) (4) DSI should provide justification for not including (b) (4) data.

- 2.3. Briefing Package Question 3: Pharmacopeial harmonization process is advancing for interchangeability of various monographs and chapters. For formulation excipients

controls, we proposed the approach for conformance to European Pharmacopeia (Ph. Eur.) requirements with adequate justification of equivalent or tighter acceptance criteria and test methods than USP (United States Pharmacopeia) monographs. Does the Agency agree with the proposed approach?

FDA Response: *We agree with this approach in the briefing package.*

Meeting Discussion: There was no further discussion on this topic.

- 2.4. **Briefing Package Question 4:** DSI is currently performing the in vitro dissolution testing of HCTZ active ingredient component for CS-8635 Tablets for the registration stability test program with two time points, specifically a 30 minutes terminal time point and an additional 15 minutes time point as requested by the FDA. We are of the opinion that the terminal time point of 30 minutes is adequate to characterize product quality and two-point testing for immediate release drug are justified for development phase purposes not for NDA release and stability testing (validation and annual batch stability programs)

For unit with the terminal time points for the other two active components analyzed, DSI intends, therefore, to have only one time point, specifically 30 minutes, as a proposed NDA acceptance criterion in the dissolution specification for release and stability testing. Does the Agency agree with this approach?

FDA Response: *Yes, a single time point dissolution specification for all three active ingredients (HCTZ, AML and OM) using a properly validated dissolution methodology is acceptable*

Meeting discussion: (Slide 3) The Agency clarified that the time used for the single time point dissolution specification may differ from one drug substance to another. The specification will be determined during the review based on the data provided. The agency may request additional information as needed during the review.

- 2.5. **Briefing Package Question 5:** DSI will be seeking market approval of 2 alternate HDPE bottle packaging systems at the time of NDA approval. The packaging system for the ICH registration stability studies contains desiccant package component while the packaging system for the supportive stability does not. Stability monitoring assessments will demonstrate protection and quality of the drug product will be maintained over the proposed shelf life in both bottle packaging systems. Is the approach for qualification and market approval of the alternate packaging systems acceptable to the Agency?

FDA Response: *The packaging configuration without desiccant is the higher risk packaging configuration. Primary stability should be conducted with this higher risk configuration if it is intended for marketing*

Meeting discussion: (Slides 7 & 8) DSI presented a proposal for a comparability protocol to evaluate the product without desiccant. The Agency agrees that a comparability protocol is an acceptable approach. The protocol should include what data will be evaluated, and the evaluation criteria (with any statistical approaches). The criteria should include the same specification and shelf-life as the to-be marketed

product. Furthermore, the Agency recommends that a minimum of 6 month accelerated data be included. The appropriate filing category will be evaluated at the time of the review.

- 2.6. **Briefing Package Question 6:** At the time of NDA submission, a primary stability database of a minimum of 12 months real time and 6 months accelerated, site specific data under ICH conditions will be available for a total of fourteen (14) batches of bulk drug product. Does the Agency agree to accept the submission of updated stability before month 5 of the review cycle, and the report does not constitute a major amendment an extension of the review clock?

FDA Response: *The Agency agrees to accept the submission of updated stability before the five months review cycle for the primary registration batches only.*

Meeting Discussion: (Slide 3) DSI would like to provide additional stability data for the bulk tablets during the submission and will provide updated stability data at the 5 months review cycle. The Agency agrees that this is acceptable and will be reviewed as part of the submission.

- 2.7. **Briefing Package Question 7:** DSI proposes the extension of expiry dates based on pilot registration drug product batches with accumulated real time data and to submit a Prior Approval Supplement (PAS) for expiration period extension. Does the Agency agree with this approach?

FDA Response: *The Agency agrees with this approach.*

Meeting Discussion: There was no further discussion on this topic.

- 2.8. **Briefing Package Question 8:** Is the approach of providing on authorized condensed English translation copy of the original executed batch record for each of the five different strengths of drug product intended for market acceptable to the Agency?

FDA Response: *The Agency will need at least one original batch record and its complete English translation.*

Meeting Discussion: (Slide 3) DSI indicated that there will be one executed batch record for one strength, and the translation will be complete. The Agency agrees.

3. ADDITIONAL COMMENTS/ISSUES REQUIRING FURTHER DISCUSSION

None

4. ACTION ITEMS

There were no actions items from this meeting

5. CONCURRENCE:

{See appended electronic signature page}

Don Henry
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Christine Moore, Ph.D.
Acting Division Director
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

6. ATTACHMENTS:



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Linked Applications

Sponsor Name

Drug Name / Subject

IND 77651

DAIICHI SANKYO INC

CS8635 TABLETS

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/s/

DON L HENRY

05/01/2009

CHRISTINE M MOORE

05/01/2009

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
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Transmitted to fax: (732) 906-6652
Attention: Mr. Tetsuya Kaiso
Sponsor: Daiichi-Sankyo
Phone: (732) 590-4945
Subject: **IND 77,651**
Meeting Minutes
Date: September 7, 2007

Pages including this sheet: 15

From: Denise M. Hinton
Phone: 301-796-1090
Fax: 301-796-9838
E-mail: Denise.Hinton@fda.hhs.gov

IND 77,651

**Type C Guidance Meeting between the FDA and Daiichi-Sankyo
CS-8635 (olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide) Tablets**

Meeting Date:	July 24, 2007
Application Number:	IND 77,651
Sponsor:	Daiichi-Sankyo, Inc.
Drug:	CS-8635 Tablets (olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide)
Type of Meeting:	Type C
Classification:	Guidance
Meeting Request Date:	May 9, 2007
Confirmation Date:	May 11, 2007
Briefing Document Date:	June 26, 2007

FDA List of Attendees:

Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Division Director
Thomas Marciniak, MD	Team Leader, Medical Officer
Lydia Velazquez, PharmD	Clinical Pharmacologist
Charles Resnick, PhD	Team Leader, Pharmacologist
Albert DeFelice, PhD	Team Leader, Pharmacologist
James Hung, PhD	Team Leader, Statistician
Steven Bai, PhD	Statistician
Edward Fromm	Chief, Project Management Staff
Denise Hinton	Project Management Staff

Daiichi Sankyo Pharma Development

Howard Hoffman, MD,	Vice President, Regulatory Affairs
Rich Cuprys,	Executive Director, Regulatory Affairs
Tetsuya Kaiso,	Manager, Regulatory Affairs
Reinilde Heyrman, MD,	Executive Director, Clinical Development
Michael Melino, PhD,	Director, Clinical Development
Jane Li, MD,	Senior Director, Risk Management
Antonia Wang, PhD,	Senior Director, Biostatistics
Prachi Wickremasingha, Pharm D,	Associate Director, Translational Medicine and Clinical Pharmacology
SaeHeum Song, PhD	Associate Director, Translational Medicine and Clinical Pharmacology

Background

Daiichi-Sankyo requested this meeting to discuss and gain agreement on the adequacy of the development program for CS-8635, the triple fixed dose combination of olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide. The proposed indication is for the treatment of hypertension. Preliminary comments were provided to the sponsor on July 13, 2007 in preparation for the face-to-face meeting.

Discussion

Following introductions, the sponsor presented the attached slides with updates to the July 13, 2007 preliminary responses that addressed the adequacy of the clinical, clinical pharmacology, and characterization of hydrochlorothiazide product to be used in the clinical program. The sponsor was in full agreement with our responses related to the adequacy of their proposed safety, non-clinical program, and the pediatric waiver request.

Questions and Responses

Adequacy of the Clinical Program

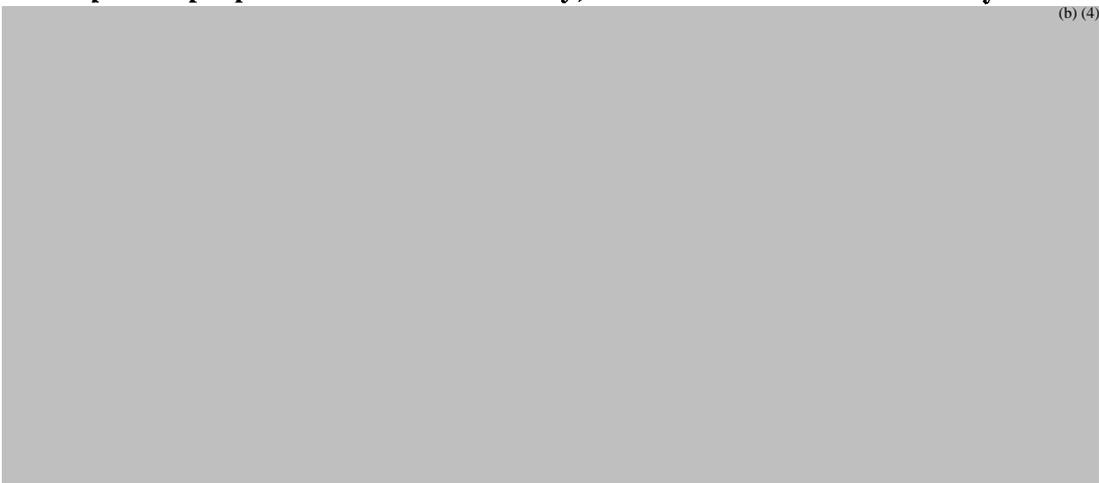
1. Efficacy of the triple combination with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide will be provided by the proposed two (b) (4), factorial trials. Does the FDA concur this is sufficient to support registration for a triple combination product?

FDA Preliminary Response:

No, we do not concur that the two studies are sufficient to support registration for a triple combination product. What is lacking is a study demonstrating that OM adds to the hypertensive effect of AML/HCTZ. Rather than three large factorial studies what we would prefer is a single study demonstrating that the antihypertensive effect of a triple combination (could be highest dosages but doesn't have to be) is superior to those of each double combination at highest dosages, i.e., OM/AML 40/10, OM/HCTZ 40/25, and AML/HCTZ 10/25.

Discussion during Face to Face Meeting

The Sponsor proposed an alternative study, which was referred to as Study A.



(b) (4)

Dr. Stockbridge stated that the sponsor's newly proposed approach is acceptable; however, he recommended that they show that the antihypertensive effect of one triple combination is superior to each double combination at the highest dosages. He thought the 40/10/25 mg dose would beat the high-dose pairs. The Division advised the Sponsor that if a triple dose combination shows superiority to each of the highest double combinations, lower dose triple combinations could be marketed without being studied in this program. The Division indicated that the lower dose triple combinations could be further supported by modeling and simulation data.

The Sponsor asked if

(b) (4)

The Division indicated that this approach was not acceptable and that the triple dose combination needed to be superior to all three of the double combinations.

The Division indicated that it would be possible to have double primary endpoints both for efficacy and safety in the study. However, all safety primary endpoint must be pre-specified and sufficiently powered for comparison.

The Division indicated that a placebo arm would not be required in the program. However, it was recommended that the Sponsor minimize regression to the mean effects, and "white coat" hypertension by having separate screening or qualifying and baseline measurements.

The Division indicated that it would be acceptable to enrich the population as per the following example:

- **Including patients with more severe hypertension**
- **DBP \geq 100 mmHg**
- **Daytime ABPM mean DBP \geq 100 mmHg**
- **Randomizing only non-responders to dual combination**

The sponsor also asked if

(b) (4)

be approvable?

The Division stated it is likely that the above proposal could be approved based on the predicate assumption; however it would be dependent on the review and description of the results.

2. The Statistical Analyses in the Protocol Synopses for studies A and B outlines the statistical methodology and power statement rationale. Does the FDA concur with the

proposed statistical plan?

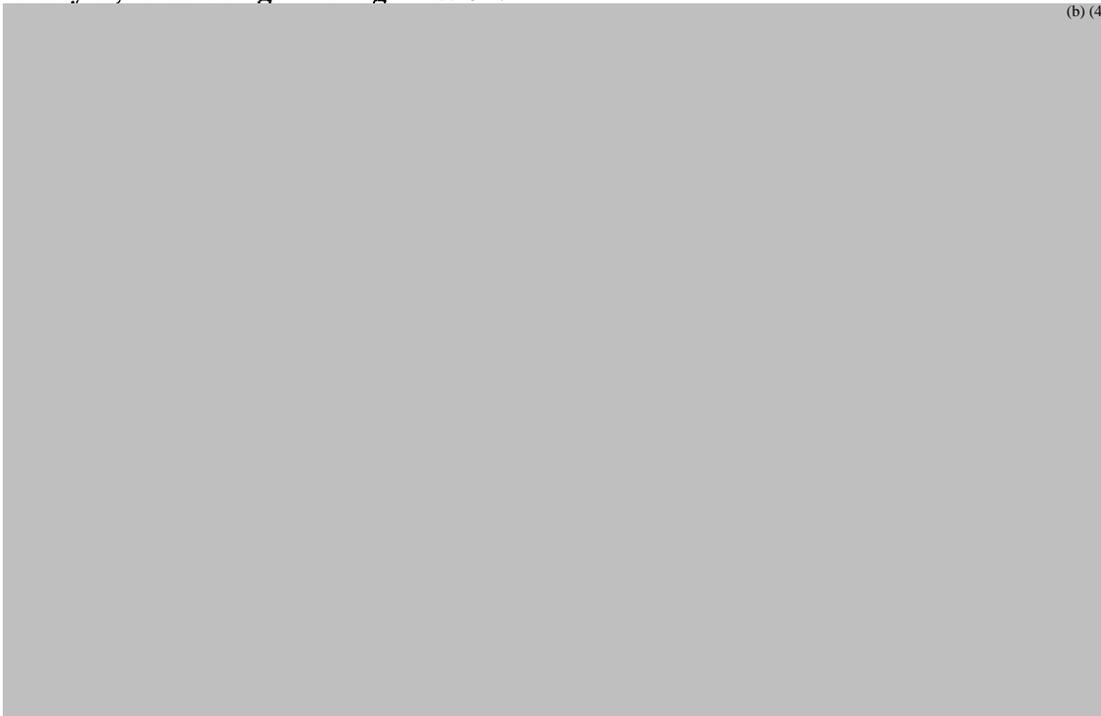
FDA Preliminary Response:

Response surface analysis for a triple combination is problematic. We require demonstrating the superiority of the triple combination to each of the double combinations at highest dosages as discussed in response 1.

Discussion during Face to Face Meeting

In addition to the response above, the Division proposed consideration of an alternative statistical testing strategy, i.e., pre-specify the majority of the alpha to a few higher triple dose combinations to be tested under Holm's procedure and the rest of the triple dose combinations to be tested in a pre-specified order using a step-down procedure utilizing the remaining alpha. The Division commented that there is no requirement to pre-specify the sequence of the few higher triple dose combinations that will consume the majority of the alpha.

The Sponsor proposed a second alternative study, which was referred to as the Study B, to enable global registration:



The Division indicated that it is the Sponsor's decision as whether to add additional triple dose combination arms. The Division is also open to different statistical approaches and primary endpoints in the same study to satisfy filings in both the US and Europe; however, from our point of view, the study does not have to have the same endpoints in the US as in Europe. The Sponsor may submit the pivotal trial protocol as a special protocol assessment.

3. Daiichi Sankyo does not intend to market the following triple FDCs (b) (4)

The proposed clinical studies A and B do not include evaluation of these triple FDCs. If information on these FDCs is required, it would be obtained using pharmacodynamic modeling and simulation techniques. The detailed plan of modeling and simulation is described in the section Adequacy of Clinical Program, item 6 on page 24 of the briefing document. Does the FDA concur with this proposal?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

4. Assuming that the proposed studies A and B (b) (4)

. If yes, would the proposed factorial studies suffice to obtain such an indication?

If no, does the FDA have any special recommendations or study design considerations for when the Sponsor if the Sponsor plans to pursue an indication for (b) (4)

FDA Preliminary Response:

Please refer to the discussions at the recent Cardiovascular and Renal Drugs Advisory Committee meeting on April 18. However, justifying (b) (4) will be difficult.

a) Please see response 1 regarding the proposed factorial studies.

b) We would need to discuss justifications for (b) (4).

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

5. The sponsor intends to conduct PK/PD substudies in the two pivotal studies with blood pressure measurements and PK samples obtained at 0.5-2hours, corresponding to the peak of OM and HCTZ, and 5-10 hours, corresponding to the peak of AML, after dosing. The blood pressures measured at these time intervals together with trough blood pressure measured at the visit will be used to estimate the trough/peak ratio. Does the FDA concur?

FDA Preliminary Response:

We concur that PK/PD measurements at 0.5-2 hours and 5-10 hours are reasonable. We do need to know the sizes of these substudies before concluding that they are adequate. In addition, you should also perform an ABPM substudy to characterize the effects of the triple combination compared to the doubles throughout the interdosing interval.

Discussion during Face to Face Meeting

The Sponsor asked for clarification on the key objectives of performing ABPM measurements. The Division responded that they were interested in understanding the effects of the triple dose combination compared to the double dose combinations throughout the entire dosing interval. The Division indicated that their objective might be addressed through PK/PD, ABPM, or both and agreed to review a specific proposal from the Sponsor to address their question.

6. The sponsor intends to use a validated automated oscillometric device to measure sitting blood pressure in the investigator's office. Does the FDA concur with use of this type of device?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

7. The sponsor plans to submit a 24 week interim report at the time of NDA submission, followed by a submission of additional safety data at the time of 4 month safety updates. Does the FDA concur with this plan?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

The Sponsor agreed with the FDA preliminary response. Based on adequate data supporting the safety of monotherapy with OM, AML and HCTZ, as well as the dual combinations of OM/AML or OM/HCTZ, the Sponsor asked the Division's opinion on providing less than 24-week data at the time of NDA submission (b) (4). The Division indicated that it would consider a proposal from the Sponsor.

Adequacy of Safety Program

1. Long-term safety information will be collected in approximately 550 patients for one (1) year period. Daiichi-Sankyo proposes that the 6 month long-term safety data on 1000 patients be included in the NDA submission. Daiichi Sankyo believes that the extent and duration of patient exposure from the clinical program would be sufficient, pending review, to support filing and registration. Does the FDA concur?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

2. Daiichi Sankyo believes that the inclusion of approximately 280 patients over 65 years old is sufficient for the NDA filing. Does the FDA concur?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

3. Safety in the highest dose group (OM 40 mg/ALM 10 mg/ HCTZ 25 mg) will be provided [REDACTED] ^{(b)(4)}. Additional exposure to this FDC will be obtained from patients enrolling in the open-label period from both factorial design studies. Does the FDA agree that this is sufficient to evaluate safety in the highest dose group?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

4. Safety of anti-hypertensive treatment-naïve patients or patients washed out of previous anti-hypertensive treatment, who are exposed to the triple combination of OM/ALM/HCTZ including the highest dose (OM 40 mg/ALM 10 mg/ HCTZ 25 mg) will be monitored as for patients in other treatment arms (i.e. vital signs, cuff BP, TEAEs, SAEs, 12-lead EKGs and laboratory tests). Daiichi Sankyo believes this is sufficient to address potential/theoretical safety issues of hypotension. Does the FDA concur?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

5. Based on adequate data supporting the safety of monotherapy with OM or AML, as well as dual combination of OM/AML or OM/HCTZ, Daiichi Sankyo does not intend to conduct centralized EKG readings or conduct any additional clinical QT/QTc studies. Does the FDA concur?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

Adequacy of Clinical Pharmacology Program

Does the FDA agree that the studies proposed address the identified main objectives of the clinical pharmacology program presented in Section 3, page 22 of the briefing document?

FDA Preliminary Response: The bioequivalence with the highest dose may not be sufficient. You may need to conduct an additional bioequivalence study with the lower dose. This will depend on the composition of your final market image formulation and whether it is compositionally dose proportional

Discussion during Face to Face Meeting

No further discussion; the Division agreed to have additional discussions in the future with the Sponsor related to clinical pharmacology and CMC matters as the development program progresses.

Does the FDA agree with the clinical pharmacology plan for establishing and validating the exposure-response relationship presented in item 6 on page 24?

FDA Preliminary Response: It is not required for you to establish and validate the exposure-response relationship for this FDC.

Discussion during Face to Face Meeting

No further discussion; the Division agreed to have additional discussions in the future with the Sponsor related to clinical pharmacology and CMC matters as the development program progresses.

The highest dose strength, 40/10/25mg (OM/AML/HCTZ), will be evaluated in a planned study to establish the bioequivalence of the market image formulation with the formulation used in the clinical trials. Assuming dose proportionality of all strengths, Daiichi Sankyo would like to request a biowaiver for evaluating the bioequivalence of the lower strengths. Would the proposed bioequivalence study of the highest dose along with the dose proportionality study and the in vitro dissolution testing of all doses support our request for a biowaiver?

FDA Preliminary Response:

If the formulations are proportionally similar, a biowaiver for the lower strengths could be granted based on similarity of the dissolution profiles in several media.

Discussion during Face to Face Meeting

This is dependent upon the outcome of the dose proportionality study, the composition of your final market image formulation, and the formulations chosen for the clinical studies of all three drugs.

The Division agreed to have additional discussions in the future with the Sponsor related to clinical pharmacology and CMC matters as the development program

progresses.

Adequate Characterization of hydrochlorothiazide (HCTZ) product to be used in the Clinical Program

Does the FDA agree that the methods described in the briefing document to show the comparability of the HCTZ formulation to be used in the clinical studies and the reference products are adequate?

FDA Preliminary Response: This is dependent on the composition of the clinical formulation and the final market image.

Discussion during Face to Face Meeting

This is dependent on the composition of the clinical formulation and the final market image (F2 similarity comparisons). Bioequivalence studies may need to be conducted in order for the Division to know the composition of the monotherapies. We have to know whether the EU HCTZ delivers the same dose as the US HCTZ. It was recommended that the sponsor refer to the Scale-Up and Postapproval Changes for Immediate Release Dosage Forms -- Guidance for Industry and to have additional discussions to address this matter further if necessary.

Adequacy of Non-clinical Program

Daiichi Sankyo plans to conduct one non-clinical study, a 3-month repeated-dose toxicity study in one species (rat) with the approach of adding AML to OM/HCTZ combination, in order to address any safety concerns regarding synergistic or new toxic effects of the triple combination product. The study will also include toxicokinetic evaluations. Does the FDA agree with Daiichi Sankyo proposal to conduct one non-clinical study?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

Adequacy of Pediatric Waiver

Daiichi Sankyo respectfully requests that a waiver be granted for studying pediatric populations. Does the FDA agree with this proposal?

FDA Preliminary Response: Yes

Discussion during Face to Face Meeting

No further discussion; the Sponsor agreed with the FDA preliminary response.

Meeting Recorder: *{See appended electronic signature page}*
Denise M. Hinton

Chair Concurrence: *{See appended electronic signature page}*

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

/s/

Denise Hinton
9/7/2007 05:25:46 PM

Norman Stockbridge
9/10/2007 12:04:30 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 200175 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: TRIBENZOR Established/Proper Name: olmesartan, amlodipine, HCTZ Dosage Form: Tablets		Applicant: Daiichi-Sankyo Agent for Applicant (if applicable):
RPM: Russell Fortney		Division: Division of Cardiovascular and Renal Products
<p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s): NDA 19787 Norvasc</p> <p>Provide a brief explanation of how this product is different from the listed drug. TRIBENZOR is a combination drug product that includes three different antihypertensive drugs.</p> <p>If no listed drug, explain. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 7/23/10</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>7/31/10</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	7/23/10
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP, 7/23/10
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	7/23/10
<ul style="list-style-type: none"> Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> Example of class labeling, if applicable 	Amlodipine, olmesartan and HCTZ individual labels, and the Exforge HCT triple combination label

³ Fill in blanks with dates of reviews, letters, etc.
Version: 7/8/10

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	7/2/10
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	6/15/10, 3/29/10, 1/26/10 6/10/10, 3/8/10, 1/26/10
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 6/4/10 <input checked="" type="checkbox"/> DRISK 7/1/10 <input checked="" type="checkbox"/> DDMAC 6/21/10 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD 6/21/10
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	12/10/09
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 7/23/10 <input type="checkbox"/> Not a (b)(2) 7/23/10
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>6/2/10</u> If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	6/7/10 (2), 6/5/10, 3/29/10, 3/26/10, 1/26/10, 10/9/09, 7/9/09

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 7/8/10

❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg 7/9/09 preliminary responses
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	pre-NDA CMC Mtg 5/1/09, Clinical Guidance Mtg 7/24/07
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/19/10
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/15/10
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	4/22/10
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 8 of Medical/Statistical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A <input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 7/2/10

⁵ Filing reviews should be filed with the discipline reviews.
Version: 7/8/10

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4/22/10
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 6/28/10
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 6/28/10
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)		<input type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4/20/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 10/27/09
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None 3/31/10, 5/18/10, 7/8/10, 7/16/10
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	5/14/10
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 3/15/10 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

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

/s/

RUSSELL FORTNEY
07/23/2010