

7/21/06

FDA Preliminary Responses to
Questions in June 26, 2006 Meeting Package
for IND 70,410

Sponsor: Daiichi-Sankyo Pharma Development
Subject: End of Phase 2 CMC Meeting Question Responses
Date: July 27, 2006
Time: 1:30 p.m. - 2:30 p.m. EDT
Location: CDER White Oak 1417 Conference Room
10903 New Hampshire Ave
Silver Spring, MD 20993

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 27, 2006, 1:30 p.m. - 2:30 p.m. EDT, CDER White Oak 1417 Conference Room between Daiichi-Sankyo Pharma Development and the Center for Drug Evaluation and Research. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Scott N. Goldie, Ph.D., Regulatory Health Project Manager, (301) 796-2055). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

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1. Is this approach to employ the Ph. Eur. Monograph standard and general chapter <5.4> for drug substance controls acceptable to the Agency for the alternate sourcing of the API?

FDA Preliminary Response: We do not agree with your proposal as specified in the meeting package since Ph. Eur. is not considered an official compendium by FDA. Justification for acceptance criteria should be provided based on actual data, scientific rationale, and FDA and ICH guidelines. Specifically we recommend that you:

1. Set residual solvent limits on the basis of actual data and not on maximum limits specified in ICH guidelines.
2. Demonstrate equivalency of particle size distribution characteristics between supplied drug substance. Also, demonstrate the equivalency of drug product regardless of drug substance supplier based on dissolution.

b(4)

- 2.1 Does the Agency concur that the stability protocol agreed to verbally by FDA for primary stability batches submitted in the aforementioned amendments is sufficient for obtaining necessary stability data for CTD?
- 2.2 Does the Agency agree to accept the initial CTD with 9 months stability at the ICH conditions defined in the submitted stability study protocol?

FDA Preliminary Response: The stability protocol and initial CTD submission of 9 month stability data are acceptable as presented in the meeting package.

- 3.1 Does the Agency agree to accept and use the updated stability data from the primary studies and the interim statistical analysis report in the determination of the assigned expiry dating period for the drug product?
- 3.2 Does the Agency agree that submission of this data and report does not constitute a major amendment necessitating an extension of the review clock?

FDA Preliminary Response: Please confirm that the 4 month time referred to in the meeting package from the filing date is the date of initial submission to the FDA (stamp date). Stability data and statistical treatment can be submitted as an amendment to the NDA at any time during the review cycle. In accordance with the Good Review Management Principles Guidance (April, 2005), the quantity of data provided and the timing of the submission will determine if it will be reviewed within the first review cycle, or if the review clock would be modified.

4. Does the Agency agree to the qualification strategy for degradation products?

FDA Preliminary Response: We find the approach acceptable as described in the meeting package. We recommend that you include the chemical name and structure for all degradation products.

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5. Does the Agency agree to this approach for the establishment of the proposed in vitro test methodology and specifications for the drug product?

FDA Preliminary Response: Paddle speed of 100 rpm is not recommended by FDA or USP since the discriminating ability of the dissolution test at this high paddle speed is very limited.

b(4)

The dissolution data presented for formulation G shows that you are able observe more than 80% dissolution for both olmesartan medoxomil and amlodipine besylate at pH 6.8 in 30 minutes at 50 rpm. In light of the dissolution data from formulation G and other formulations, your rationale for the proposed dissolution testing based on dissolution data from Olmetec 40 mg and Antacal 10 mg tablets together is not appropriate.

We recommend that you provide full dissolution profiles for the proposed marketed formulation using different media and speeds with both USP Apparatus 1 and 2.

6. Does the Agency agree with the proposed approach for conformance to Ph. Eur. requirements for formulation excipient controls?

FDA Preliminary Response: In general, excipients which have not been harmonized between USP and Ph. Eur. should comply with the current USP monographs. However, Ph. Eur. monographs for excipients with equivalent or tighter acceptance criteria and test methods than USP monographs may be acceptable with adequate justification.

7. Is the approach of providing one authorized condensed English translation copy of the original executed batch record for a single drug product strength acceptable to the Agency?

FDA Preliminary Response: Please confirm that one English translation master batch record and one executed batch record from each dose strength will be submitted as described on page 56 of your meeting package.

Other FDA Comments:

b(4)

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Concurrence:

{See appended electronic signature page}

Kasturi Srinivasachar, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

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/s/

Scott Goldie
7/21/2006 12:56:40 PM
PROJECT MANAGER FOR QUALITY

Kasturi Srinivasachar
7/21/2006 02:27:40 PM
CHEMIST

Application Type and Number
SPONSOR:
PRODUCT:

Pre-NDA Meeting with Sponsor

Application Number: IND 70,410

Sponsor: Daiichi-Sankyo, Inc.

Drug: CS-8663 Tablets
(olmesartan medoxomil and amlodipine besylate)

Type of Meeting: Type B

Classification: Pre-NDA

Meeting Request Date: July 6, 2006

Confirmation Date: July 20, 2006

Meeting Date: September 13, 2006

Time: 1:00 – 3:00 PM

Place: Food and Drug Administration
White Oak
Building 22, Conference Room 1417
10903 New Hampshire Avenue
Silver Spring, MD 20993

List of Attendees:

Division of Cardiovascular and Renal Products

Robert Temple, M.D.	Director, Office of New Drugs, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D.	Deputy Director
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer
Thomas Marciniak, M.D.	Team Leader, Medical Officer
Albert DeFelice, Ph.D.	Team Leader, Pharmacology
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacology/ Biopharmaceutics
John Lawrence, Ph.D.	Team Leader, Statistician
Kasturi Srinivaschar, Ph.D.	Pharmaceutical Assessment Lead, Chemistry
Denise Hinton	Project Management Staff

SPONSOR:

PRODUCT:

Daiichi-Sankyo

Howard Hoffman

Rich Cuprys

Paulette Kosmoski

Tetsuya Kaiso

Reinilde Heyrman, M.D.

Michael Melino, Ph.D.

Shashank Rohatagi, Ph.D.

Antonia Wang, Ph.D.

James Lee, Ph.D.

Andreas Teubner, Ph.D.

Wataru Takasaki, Ph.D.

Martins Adeyemo, Ph.D., DABT

Jane Li, M.D.

Vice President, Regulatory Affairs

Executive Director, Regulatory Affairs

Senior Director, Regulatory Affairs-CMC

Manager, Regulatory Affairs

Executive Director, Clinical Development

Director, Clinical Development

Senior Director, Translational Medicine and

Clinical Pharmacology

Senior Director, Biostatistics

Staff Biostatistician, Biostatistics

Vice President, Pharmaceutical Development

Senior Chief Researcher, Medicinal Safety

Research Laboratories

Director, Medicinal Safety

Senior Director, Risk Management

b(4)

Upon your arrival, please ask the security guards to contact me or Mr. Anthony Baldwin at (301) 796-1037.

Best regards,

Denise M. Hinton

Regulatory Health Project Manager

Division of Cardiovascular and Renal Products

Center for Drug Evaluation and Research

Food and Drug Administration

Office (301) 796-1090

Fax (301) 796-9838

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/s/

Denise Hinton
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,410

Daiichi Sankyo Pharma Development
Attention: Paulette F. Kosmoski, Senior Director, Regulatory Affairs - CMC
399 Thornall Street
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-8663 Tablets, (olmesartan medoxomil and amlodipine besylate).

We also refer to your May 16, 2006, correspondence, received May 17, 2006, requesting a meeting to discuss the Chemistry, Manufacturing and Controls development strategy needed to support registration of your CS-8663 tablets.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date:	Thursday, July 27, 2006
Time:	1:30 pm – 2:30 pm EDT
Location:	Food and Drug Administration 10903 New Hampshire Avenue Silver Spring, MD 20993
Tentative CDER participants:	Ramesh Sood, Branch Chief Kasturi Srinivasachar, Pharmaceutical Assessment Lead Ramsharan D Mittal, Review Chemist Denise Hinton, Regulatory Health Project Manager Scott N. Goldie, Regulatory Health Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at scott.goldie@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Scott N. Goldie, Ph.D. (301-796-2055); the division secretary, Amanda Mickley, (301-796-1713).

IND 70,410

Page 2

Provide the background information for this meeting (three copies to the IND, 15 desk copies and 1 electronic version directly to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by June 27, 2006, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Scott Goldie
5/24/2006 02:52:17 PM

Minutes of a meeting between Sankyo and the FDA Division of Cardio-Renal Drug Products

Sponsor: Sankyo Pharma Inc.
 Drug: CS-8663 (olmesartan medoxomil and amlodipine besylate)
 IND: 70,410
 Date of request: September 23, 2004
 Stamp date: September 24, 2004
 Date of confirmation: October 7, 2004
 Date of briefing document: November 18, 2004
 Date of meeting: December 20, 2004 (Sponsor request)
 Type: C
 Classification: Guidance/Development Program

Meeting chair: Norman Stockbridge, M.D., Ph.D.
 Meeting recorder: Denise Hinton

FDA Attendees:

Norman Stockbridge, M.D., Ph.D. Acting Director,
 Division of Cardio-Renal Drug Products, HFD-110
 Abraham Karkowsky, M.D., Ph.D. Medical Officer/ Team Leader, HFD-110
 Nhi Beasley, Pharm.D. Clinical Pharmacology/Biopharmaceutics, HFD-860
 Albert DeFelice, Ph.D. Pharmacology/Team Leader, HFD-110
 James Hung, Ph.D. Statistics/Team Leader, HFD-710
 Denise Hinton Regulatory Health Project Manager, HFD-110

Sankyo Attendees:

Reinilde Heyrman, M.D. Senior Director, Clinical Development
 Howard Hoffman, M.D. Executive Director, Regulatory Affairs
 Sunao Manabe, D.V.M., Ph.D. Vice President, Medicinal Safety
 Michael Melino, Ph.D. Associate Director, Clinical Development
 Daniel E. Salazar, Ph.D. Executive Director, Pharmacology and Pharmacokinetics
 Antonia Wang, Ph.D. Senior Director, Biostatistics
 Jeffrey Warmke, Ph.D. Senior Director, Global Project Management
 Wataru Takasaki, Ph.D. Senior Chief Researcher, Medicinal Safety Research Laboratories

Background:

Sankyo Pharma Development requested this meeting to obtain agreement on the adequacy of the development program for CS-8663 (olmesartan medoxomil and amlodipine besylate) Tablets to support NDA approval for treatment of hypertension. The fixed dose combination drug is not indicated for the initial therapy of hypertension.

As presented in the briefing document, dated November 18, 2004, the Sponsor is planning to conduct one double-blind, placebo-controlled, factorial study evaluating the efficacy and safety of co-administration of olmesartan medoxomil plus amlodipine besylate compared to monotherapy in patients with mild to severe hypertension. The dose-ranging study is designed to assess the antihypertensive efficacy of different dose combinations of olmesartan

medoxomil/amlodipine besylate in comparison to the respective monotherapy, at the same dose level. The study will have 12 parallel groups: placebo; olmesartan medoxomil 10, 20 and 40 mg; amlodipine besylate 5 and 10 mg; and all possible combinations of these two therapies. Study participants will be given the option to proceed into an open-label long-term extension after the double-blind portion of the study to obtain information on long-term safety and tolerability for up to one year.

Discussions:

The Division responded to the Sponsor's questions as follows:

- 1. Efficacy of the olmesartan/amlodipine combination will be provided by the proposed large, single 1260 patient, factorial trial. Does the FDA concur this study is sufficient to support registration?**

FDA response: The Division stated that the study is sufficient to support registration and offered suggestions for improvement. It was recommended that the Sponsor assess whether people can tolerate a higher dose of amlodipine in the presence of olmesartan by adding four more cells with 20 mg of amlodipine alone and in combination with various other doses. Edema usually limits dose on amlodipine, but not the blood pressure effect and if it shown that olmesartan decreases the incidence of edema then the Sponsor can seek a claim for it.

The Sponsor voiced concern over the potential blood pressure effects with the high dose and stated that they do not intend to change the label. The Division addressed their concern and recognized that going to high dose may cause a tolerance problem and have a negative effect on the primary analysis. They were encouraged to think about not enrolling people with minimum hypertension or in groups with high dose amlodipine and to do a titration scheme of 10 people in the first two weeks and 20 in the last two weeks. There will be no repercussions in the label if there is a series of adverse events resulting from testing at high dose (20 mg amlodipine combination). It was recommended that the Sponsor keep the primary hypothesis based on 12-cell factorial proposed and if successful, then they should test to 16 cells to protect the study. This will allow for adequate dosing information with the combination product and may generate less edema. To address the edema endpoint, the Sponsor was advised to use measure of clinical edema with adverse events or discontinuation due to edema.

In regard to the double-blind 8-week study with the main focus on safety, the Division stated it was hard to interpret because it lacked a monotherapy or placebo group in weeks 8-16 and Phases 3 and 4 did not offer helpful information. It would be more beneficial to have longer term exposure data and it would be acceptable to conduct a 6-week double-blind trial and carry it forward to an open label trial of a reasonable duration for an adequate titration scheme.

b(4)

They were asked to consider 12 cells in period 2 then qualify people to period 3 with the 40/20 mg dose. Better safety data could be generated

if people are assigned to a treatment algorithm and placebo controlled group in an 8-week double blind and 4-week open-label study.

2. **The Protocol Profile Statistical Plan (section 5.6 of the briefing document) outlines the study methodology and rationale for power statement. Is FDA in agreement with the proposed statistical plan?**

FDA response: The Division stated the proposed statistical plan is acceptable and suggested that the Sponsor also consider using ANOVA for their analysis. The Sponsor stated that they did use ANOVA initially, but did not think it would make a major difference. The Division stated that their conservative analysis is adequate, but could be improved by generating the primary analysis with ANOVA first and if the data shows non-additivity (particularly negative interaction or sub-additivity) then they could use their average test. Another suggestion was to use an unbalanced design, load up some cells and focus hypothesis testing on these particular cells instead of the whole factorial. The Sponsor stated they would present the proposals in Europe to see if the recommended ANOVA approach would be acceptable.

3. **Both olmesartan medoxomil and amlodipine are compounds with well established dosing regimens of once daily administration. The trough to peak ratio for olmesartan medoxomil for systolic and diastolic response is between 60 and 80%. The Product insert for amlodipine indicates that maintenance of the blood pressure effect over the 24 hour dosing interval was observed, with little difference in peak and trough effect. Sankyo believes this is adequate information to provide for once-daily dosing of the combination and little additional information will be obtained by measuring peak effect. Sankyo proposes to evaluate only trough diastolic and systolic blood pressure. Does the FDA concur with this approach?**

FDA response: The Division stated that peak data would be useful for understanding safety and indicated that sparse data (centers, ABPM trial, sparse PK sampling, etc) would help to inform people about an adequate time course. The Sponsor was advised to use sparse PK sampling in part of the population or conduct an ambulatory blood pressure study with 10-20 patients from each cell. Peak data should be collected over a wider window of time to reflect the time of peak effect for olmesartan and amlodipine. The Division will look at the exposure response over time and is interested in the highest doses studied (40/20 mg and 40/10mg). The Sponsor stated they would examine peak effects in an appropriate amount of patients.

4. **The safety program described will provide adequate numbers of patient exposure to support approval. Does the FDA concur?**

FDA response: The Division concurs and stated that there is more than adequate patient exposure.

- 4a. **Safety in the elderly will be provided by >200 patients over the age of 65. Does the FDA concur that this is adequate?**

FDA response: The Division concurs that the numbers are adequate and received confirmation that the PK effect of olmesartan showed no change in PK. Since there is an increase in AUC with renal dysfunction and amlodipine has a doubling of AUC in the elderly, the results will be described in labeling. Comparative statements will not be included in the labeling if there are inadequate numbers of elderly patients to make statistical comparisons to the larger group.

4b. Does FDA concur that this exposure at the highest dose level is adequate?

FDA response: The Division concurs that exposure at the highest dose level is adequate and it will be acceptable to get to olmesartan 40 mg/ amlodipine 20 mg if the Sponsor chooses to do so.

4c. Does FDA concur that this will provide adequate long-term safety data for registration?

FDA response: The Division concurs that long-term safety data is sufficient for registration.

5. Based on this data and the clinical safety of monotherapy with olmesartan medoxomil and amlodipine besylate, Sankyo does not intend to conduct clinical QT/QTc trials. Does the FDA concur?

FDA response: The Division concurs and asks that the sponsor submit the post-marketing data for the cause/occurrence of Torsades de Pointes.

6. Does the agency concur that the proposed non-clinical study will suffice?

FDA response: The proposed non-clinical study is sufficient. The Sponsor was asked to demonstrate toxicity on monotherapy and in combination prior to deciding on dosing in the definitive study. They agreed to submit their final protocol with rationale to the Agency for review.

7. Does the FDA concur that the proposed clinical pharmacology program together with the extensive clinical pharmacology information already available from the olmesartan medoxomil and amlodipine besylate programs for monotherapy will support the registration of olmesartan/amlodipine?

FDA response: The information from the proposed programs will support the registration of olmesartan/amlodipine and if the 40/20 mg dose is used, it will be necessary to conduct a PK study at the highest doses. The Sponsor agreed with the Division's request to submit the final protocol in the IND.

8. Does the FDA agree with the assumption that a 505(b) 2 application is adequate for this fixed dose combination of olmesartan medoxomil and amlodipine?

Draft: 3Jan05
Final: 13Jan05

RD:
Beasley 1/10/05
DeFelice 1/10/05
Hung 1/11/05
Karkowsky1/13/05
Stockbridge 1/12/05

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Denise Hinton
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Norman Stockbridge
1/13/05 04:07:34 PM

10/07/04

Meeting Confirmation

Sponsor: Sankyo Pharma Inc.
 Drug: CS-8663 (olmesartan medoxomil and amlodipine besylate)
 IND: 70,410
 Date of request: September 23, 2004
 Stamp date: September 24, 2004
 Date of confirmation: October 7, 2004
 Date of meeting: December 20, 2004 (Sponsor request)
 Time: 10:30 – 12:00 PM
 Place: WOC 2, 5th Floor, Conference Room F
 1451 Rockville Pike
 Rockville, MD
 Type: C
 Classification: Guidance/Development Program

FDA Attendees:
 Norman Stockbridge, M.D., Ph.D. Acting Director,
 Division of Cardio-Renal Drug Products, HFD-110
 Abraham Karkowsky, M.D., Ph.D. Medical Officer/ Team Leader, HFD-110
 Patrick Marroum, Ph.D. Clinical Pharmacology/Biopharmaceutics Team Leader, HFD-860
 Albert DeFelice, Ph.D. Pharmacology/Team Leader, HFD-110
 Kasturi Srinivasachar, Ph.D. Chemistry/Team Leader, HFD-110
 James Hung, Ph.D. Statistics/Team Leader, HFD-710
 Charles Le, Ph.D. Statistician, HFD-710
 Denise Hinton Regulatory Health Project Manager, HFD-110

Please provide 12 briefing documents at least 4 weeks prior to the meeting.

Please ask the security guard to call Mr. Anthony Baldwin at (301) 594-5367 upon arrival.

Thank you,

Denise M. Hinton
 Regulatory Health Project Manager, HFD-110
 Division of Cardio-Renal Drug Products
 Center for Drug Evaluation and Research
 Food and Drug Administration

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Denise Hinton
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9/30/04

MEMORANDUM

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

DATE: September 30, 2004
FROM: Denise M. Hinton, HFD-110
SUBJECT: **IND 70,410**
CS-8633 (olmesartan medoxomil and amlodipine besylate)
Tablets)

Sankyo Pharma Development submitted a IND on August 13, 2004 for CS-833, a fixed-dose combination of the two approved drugs Benicar (olmesartan medoxomil) Tablets and Norvasc (amlodipine besylate). The proposed indication is the treatment of essential hypertension.

Per Dr. Abraham Karkowsky, no safety meeting was necessary for this IND as both drugs are FDA approved and there are no safety concerns. The pharmacology and clinical pharmacology and biopharmaceutics reviews are in DFS.

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Denise Hinton
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CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-100 Supplement # Efficacy Supplement Type SE-

Proprietary Name: AZOR
Established Name: amlodipine besylate and olmesartan medoxomil) Tablets
Strengths: 5/20, 5/40, 10/20, 10/40 mg

Applicant: Daiichi Sankyo Inc.
Agent for Applicant (if applicable): NA

Date of Application: November 27, 2006
Date of Receipt: November 27, 2006
Date clock started after UN: NA
Date of Filing Meeting: January 18, 2007
Filing Date: January 26, 2007
Action Goal Date (optional): September 26, 2007 User Fee Goal Date: September 27, 2007

Indication(s) requested: AZOR is indicated 1) either alone or in combination with other antihypertensive agents for the treatment of hypertension and for 2) initial therapy in patients with hypertension requiring blood pressure reduction .

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

NOTE:

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

Review Classification: S X P
Resubmission after withdrawal? No Resubmission after refuse to file? No
Chemical Classification: (1,2,3 etc.) 4S
Other (orphan, OTC, etc.) NA

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

User Fee Status: #PD3006796 Paid X Exempt (orphan, government)
Waived (e.g., small business, public health)

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

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

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES X NO
If yes, explain: The patent for NDA 19-787/Pfizer's Norvasc (amlodipine besylate) 2.5, 5, and 10 mg Tablets will expire on March 25, 2007, September 26, 2007 (Pediatric Exclusivity)

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

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

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

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

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

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

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

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

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

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

1. This application is a paper NDA YES No X

2. This application is an eNDA or combined paper + eNDA YES NO X

This application is: All electronic Combined paper + eNDA

This application is in: NDA format CTD format X

Combined NDA and CTD formats

Does the eNDA, follow the guidance? N/A

(<http://www.fda.gov/cder/guidance/2353fnl.pdf>)

YES NO

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

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

Additional comments:

3. This application is an eCTD NDA. YES X
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

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

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND 70, 410
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) July 27, 2006 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) September 13, 2006 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) February 23, 2005 NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

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

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

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

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

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A X YES NO

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

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

If Rx-to-OTC Switch or OTC application:

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

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

Clinical

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

Chemistry

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

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO

- If a parenteral product, consulted to Microbiology Team? N/A YES NO

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

	N/A	X	YES	<input type="checkbox"/>	NO	<input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A	X	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
STATISTICS	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>
BIOPHARMACEUTICS			FILE	X	REFUSE TO FILE	<input type="checkbox"/>
• Biopharm. study site audits(s) needed?			YES	X	<input type="checkbox"/>	NO <input type="checkbox"/>
PHARMACOLOGY/TOX	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>
• GLP audit needed?			YES	<input type="checkbox"/>	NO	X <input type="checkbox"/>
CHEMISTRY			FILE	X	REFUSE TO FILE	<input type="checkbox"/>
• Establishment(s) ready for inspection?			YES	X	NO	<input type="checkbox"/>
• Sterile product?			YES	<input type="checkbox"/>	NO	X <input type="checkbox"/>
If yes, was microbiology consulted for validation of sterilization?	N/A		YES	<input type="checkbox"/>	NO	<input type="checkbox"/>

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- X Filing issues to be communicated by Day 74. List (optional):

We requested that the sponsor submit the following information on February 9, 2007:

1. In accordance with CFR 314.50 (i)(1)(i)(A)(4), please submit a patent certification under Paragraph IV confirming that you own olmesartan medoxomil.
2. Provide a table cross-referencing the batch numbers to study numbers, batch size, and batch identification.
3. Submit a request for a biowaiver of bioequivalence studies for the intermediate strengths.
4. You state in your study report that the pharmacogenomics data collected for study 301 will not be submitted at this time. Please clarify why there will be a delay in submitting the data.

5. The established name, amlodipine besylate, and the strength (5 or 10 mg) do not match s _____
_____. The package insert and container labels should be revised and resubmitted
accordingly.

b(4)

On February 12, 2007, the sponsor submitted a response to our 74-day letter and addressed all the issues with the exception of item #5. In an email, dated February 14, 2007, they stated they would resubmit the labeling as requested.

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. X Convey document filing issues/no filing issues to applicant by Day 74.

Denise M. Hinton
Regulatory Project Manager

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Appendix A to NDA Regulatory Filing Review

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 19-787 Norvasc (amlodipine besylate) 2.5, 5, and 10 mg Tablets

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO X

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO X

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

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

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES X NO

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

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

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES X NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES X NO

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

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

Pharmaceutical equivalent(s):

Norvasc (amlodipine besylate) 2.5, 5, and 10 mg Tablets

Benicar 5, 20 and 40 mg Tablets

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

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

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

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

Norvasc and Benicar (olmesartan medoxomil) are indicated for the treatment of hypertension and may be used alone or in combination with other antihypertensive agents.

The additional indication that is not included in the Norvasc or Benicar label is as follows:

Initial therapy in selected patients with hypertension requiring blood pressure reduction

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

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

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

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

Pharmaceutical alternative(s):

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

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

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

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

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

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

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO

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

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

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

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

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s): 4, 572, 909 (Peds expiration: 31Jan07)

X 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s): 4,879,303 (Peds expiration: 25Sep07)

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s): 5,616,599 and 6,878,703

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

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

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

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

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

14. Did the applicant:

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

YES NO

If "Yes," what is the listed drug product(s) NDA 19-787/Norvasc (amlodipine besylate) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug : Reports of investigations

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

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

N/A YES NO

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

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration
NDA 19-787/Norvasc	001/4879303		25Mar07
NDA 19-787/Norvasc	001/4879303	PED	25Sep07
NDA 19-787/Norvasc	001/4572909	PED	31Jan07
NDA 19-787/Norvasc	001	I-472	28Sep08

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/s/

Denise Hinton
2/26/2007 04:42:11 PM
CSO

ACTION PACKAGE CHECKLIST

NDA # 22-100	NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: AZOR Established Name: amlodipine besylate and olmesartan medoxomil Dosage Form: 5/20 mg, 10/20 mg, 5/40 mg, and 10/40 mg		Applicant: Daiichi-Sankyo Pharma Development
RPM: Denise Hinton		Division: DCRP Phone # (301) 796-1090
NDAs: 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) (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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 19-787 Norvasc (amlodipine besylate) Tablets NDA 21-286 Benicar (olmesartan medoxomil) Tablets Provide a brief explanation of how this product is different from the listed drug. Combination product <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. X Confirmed <input type="checkbox"/> Corrected Date: 21Sep07
❖ User Fee Goal Date 27Sep07 ❖ Action Goal Date (if different)		
❖ Actions		
<ul style="list-style-type: none"> • Proposed action 		X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		X None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		X Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<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"> • Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) • OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action 	<input checked="" 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"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<p>X Included</p>
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/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> • NDAs: 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>) • NDAs: 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>) • NDAs: 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>) 	<p>X No <input type="checkbox"/> Yes</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p>
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	
<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. 	<p>X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<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. • [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). 	<p>21 CFR 314.50(i)(1)(i)(A) X Verified</p> <p>21 CFR 314.50(i)(1) X (ii) X (iii)</p> <p>Paragraph III certification Date patent will expire 25Mar07 Peds exclusivity 25Sep07</p>
<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>) • [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. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p>	<p>X N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

notice of certification?

(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 to the next section below (Summary Reviews).

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).

- (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?

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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>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 Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Dr. Stockbridge Sep07 Dr. Karkowsky 29Aug07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	NA
❖ Package Insert	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	None
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	Included (24Sep07)
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Included (27Nov06)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Included
❖ Patient Package Insert	
<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> Most-recent division-proposed labels (only if generated after latest applicant submission) 	None
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	24Sep07
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS 20Sep07 <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 30Apr07 <input checked="" type="checkbox"/> SEALD 29Aug07 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	RPM/Filing review 26Feb07
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	NA
❖ Pediatric Page (all actions)	X Included
❖ 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>)	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	NA
<ul style="list-style-type: none"> Incoming submission documenting commitment 	NA
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	NA
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	X No mtg 13Sep06
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	X No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	CMC 27Jul06
❖ Advisory Committee Meeting	X No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	NA
CMC/ Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	Initial Quality Assessment: 23Jan07 CMC 1: 9Aug07 CMC 2: 7Sep07 Establishment Report: 18Sep07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	X None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes. <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	9Aug07
<ul style="list-style-type: none"> <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	NA
<ul style="list-style-type: none"> <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	NA
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	X Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> NDAs: Facilities inspections (include EBR printout) 	Date completed: 13Sep07 X Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	NDA review: 8Aug07 IND: Repeat Dose Tox: 25Oct05 Initial IND review: 10Sep04
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	None
❖ Nonclinical inspection review Summary (DSI)	X None requested
❖ Clinical review(s) (<i>indicate date for each review</i>)	9Aug07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	9Aug07/page 80
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	X None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	X Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	None
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	None
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	X Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	X None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2Jul07
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None #1 26Jul07 #2 5Sep07

Appendix A 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:

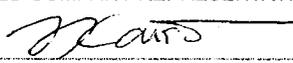
- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval 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 Office of Regulatory Policy representative.

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG USER FEE
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>DAIICHI SANKYO INC Tetsuya Kaiso 399 THORNALL STREET EDISON NJ 08837 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>022100</p>			
<p>2. TELEPHONE NUMBER</p> <p>732-590-4945</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>			
<p>3. PRODUCT NAME</p> <p>amlodipine besylate and olmesartan medoxomil tablets</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006796</p>			
<p>7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.</p> <p><input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)</p> <p><input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act</p> <p><input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE</p> <p><input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY</p>				
<p>8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>				
<p>Public reporting burden for this collection of information is estimated to average 30 minutes 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:</p> <table border="0"> <tr> <td data-bbox="259 1512 730 1638"> Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 </td> <td data-bbox="730 1512 1104 1617"> Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 </td> <td data-bbox="1104 1512 1471 1659"> 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. </td> </tr> </table>		Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.		
<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p>Tetsuya (Ted) Kaiso </p>	<p>TITLE</p> <p>Manager, Regulatory Affairs</p> <p>DATE</p> <p>November 15, 2006</p>			
<p>9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION</p> <p>\$896,200.00</p>				
<p>Form FDA 3397 (12/03)</p>				