CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022047Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

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
22-047

NAME OF APPLICANT / NDA HOLDER
AstraZeneca Pharmaceuticals LP

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)
SEROQUEL SR

ACTIVE INGREDIENT(S)	STRENGTH(S)
quetiapine fumarate	50 mg, 200 mg, 300 mg, 400 mg

DOSAGE FORM
Tablets

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 file 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	b. Issue Date of Patent	c. Expiration Date of Patent
4,879,288	11/7/1989	9/26/2011

d. Name of Patent Owner	Address *(of Patent Owner)*	
AstraZeneca Pharmaceuticals LP	1800 Concord Pike	
	City/State: Wilmington, DE	
	ZIP Code: 19803	FAX Number *(if available)*
	Telephone Number: (800) 456-3669	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)	Address *(of agent or representative named in 1.e.)*	
☞ Vice President, General Counsel & Compliance Officer AstraZeneca Pharmaceuticals LP	1800 Concord Pike	
	City/State: Wilmington, DE	
	ZIP Code: 19803	FAX Number *(if available)*
	Telephone Number: (800) 456-3669	E-Mail Address *(if available)*

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?	☒ Yes	☐ 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? * Certain claims may cover at least one additional polymorph in addition to claiming the drug substance of the pending NDA, amendment or supplement, but the patent is not being listed on that basis.	☐ Yes	☒ 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).	☐ Yes	☐ 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.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ 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.)	☐ Yes	☐ 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?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ 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.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
7	☒ Yes	☐ 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 approved labeling.)*

Schizophrenia: Seroquel SR is indicated for the treatment of schizophrenia. INDICATIONS AND USAGE

(1) INDICATIONS AND USAGE, relating to treatment of schizophrenia; (2) DOSAGE AND ADMINISTRATION, relating to treatment of schizophrenia; (3) WARNINGS AND PRECAUTIONS, relating to treatment of schizophrenia; (4) ADVERSE REACTIONS, relating to treatment of schizophrenia; (5) DESCRIPTION, relating to treatment of schizophrenia (6) CLINICAL PHARMACOLOGY, Mechanism of Action, Pharmacodynamics & Pharmacokinetics relating to treatment of schizophrenia; (7) CLINICAL STUDIES, relating to treatment of schizophrenia.

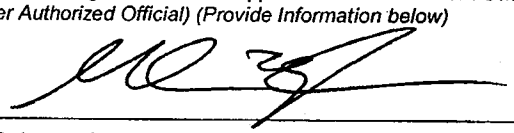
5. No Relevant Patents

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. ☐ Yes

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
	6/9/06

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 Glenn M Engelmann, Vice President, Policy, Legal & Scientific Affairs & General Counsel	
Address 1800 Concord Pike	City/State Wilmington, DE
ZIP Code 19803	Telephone Number (302) 886-3244
FAX Number *(if available)* (302) 886-1578	E-Mail Address *(if available)* glenn.engelmann@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration
CDER (HFD-007)
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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 22-047 SUPPL # -- HFD # 130

Trade Name SEROQUEL XR

Generic Name quetiapine fumarate

Applicant Name AstraZeneca Pharmaceuticals

Approval Date, If Known 5/17/07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

INFORMATION BELOW REFERS TO SE2-010 ONLY;
SLR-008 DOES NOT NEED AN EXCLUSIVITY DETERMINATION.

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 X NO ☐

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

505(b)(1)

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 X 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:

see above

d) Did the applicant request exclusivity?

YES X 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? 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?

N/A

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# 20-639 SEROQUEL IR Tablets

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#

NDA#

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:

Study 132

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 : Study 132	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: Study 132	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"): Study 132 = new

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 # 45,456	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?

NOT APPLICABLE

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: Kimberly Updegraff, B.S., M.S., R.Ph.
Title: Regulatory Health Project Manager
Date: May 17, 2007

Name of Office/Division Director signing form: Thomas P. Laughren, M.D.
Title: Director, Division of Psychiatry Products

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

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

/s/

Thomas Laughren
5/22/2007 12:36:40 PM

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

SEROQUEL® SR (quetiapine fumarate sustained-release) Tablets
NDA 22-047

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

EXCLUSIVITY INFORMATION

1. Exclusivity Claim

   AstraZeneca Pharmaceuticals LP claims an exclusivity period of three years for this New Drug Application.

2. Authority for Exclusivity Claim

   Exclusivity for this New Drug Application is being claimed pursuant to 21 CFR 314.108(b)(4).

3. Information Demonstrating this Application Contains New Clinical Investigations Conducted or Sponsored by the Applicant that are Essential to the Approval of this New Drug Application.

   (a) Certification of New Clinical Investigations

   AstraZeneca Pharmaceuticals LP certifies that to the best of its knowledge, each of the clinical investigation(s) included in this New Drug Application meets the definition of "new clinical investigation" set forth in 21 CFR Section 314.108(a).

Martin Brecher, M.D.
Executive Director, Medical Science

(b) Essential to Approval

(i) Literature Search

Attached as Exhibit A is a list of all published studies and publicly available reports of clinical investigations known to AstraZeneca Pharmaceuticals LP through a literature search that are relevant to the conditions for which approval is being sought.

(ii) Certification

AstraZeneca Pharmaceuticals LP certifies that it has thoroughly searched the scientific literature and, to the best of its knowledge, the list of relevant published studies and/or publicly available reports is complete and accurate, and in its opinion, such published studies and/or publicly available reports do not provide a sufficient basis for the approval of the conditions for which approval is being sought without reference to the new clinical investigation(s) in this New Drug Application.

Martin Brecher

Martin Brecher, M.D.
Executive Director, Medical Science

(iii) Explanation

The listed published studies and/or publicly available reports of clinical investigations do not provide sufficient basis for the approval of the conditions for which the Applicant is seeking approval, without reference to the new clinical investigations in this supplemental new drug application.

The new clinical investigations provide safety and efficacy data regarding the use of SEROQUEL® SR (quetiapine fumarate sustained-release) Tablets for the treatment of schizophrenia that could not be gleaned from published information. Accordingly, these new clinical investigations are essential to the approval of this New Drug Application.

(c) Conducted or Sponsored by the Applicant

AstraZeneca Pharmaceuticals LP, the agent and subsidiary of AstraZeneca UK Limited, is the sponsor named in Form FDA 1571 for IND 45,456 under which the new clinical investigations essential to the approval of this New Drug Application were conducted. We believe this fact is sufficient under 21 CFR 314.50(j)(4)(iii) to establish that the clinical investigations were conducted or sponsored by the Applicant.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-047 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: 17 July 2006 **PDUFA Goal Date:** 17 May 2007

HFD 130 **Trade and generic names/dosage form:** SEROQUEL XR (quetiapine fumarate) Extended-Release Tablets

Applicant: AstraZeneca Pharmacueticals LP **Therapeutic Class:** Schizophrenia

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- **X Yes. Please proceed to the next question.**
- ❑ **No. PREA does not apply. Skip to signature block.**

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Once Daily Treatment of Schizophrenia

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- **X No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- **X No: Please check all that apply:** X **Partial Waiver** X **Deferred** ____ **Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr.__0__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__12__ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☒ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._13____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._17____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☒ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:
Date studies are due (mm/dd/yy): _February 11, 2010_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:
{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Kimberly Updegraff
5/17/2007 10:53:16 AM

AstraZeneca

SEROQUEL® SR (quetiapine fumarate sustained-release) Tablets

NDA 22-047

June 5, 2006

Statement of Deferral of Pediatric Studies

1. STATEMENT OF DEFERRAL OF PEDIATRIC STUDIES

AstraZeneca Pharmaceuticals LP (AstraZeneca) is hereby providing a statement of deferral for conducting pediatric studies for this SEROQUEL® SR (quetiapine fumarate sustained-release) Tablets New Drug Application (NDA).

SEROQUEL® SR (quetiapine fumarate sustained-release) Tablets

NDA 22-047

AstraZeneca Pharmaceuticals LP (AstraZeneca)

Indication: SEROQUEL SR is indicated for the treatment of schizophrenia.

Ages Addressed in Deferral: Adolescents (ages 13-17 years)

Rationale:

The FDA has granted a deferral for the requirement of submitting pediatric data in this NDA. The deferral for conducting pediatric studies in the SEROQUEL SR clinical development program was agreed to at the June 20, 2002 pre-NDA meeting between the Division of Neuropharmacological Drug Products and AstraZeneca. The Division reconfirmed this agreement, in light of the Pediatric Research Equity Act of 2003, during a January 14, 2005 pre-sNDA meeting to discuss the SEROQUEL Bipolar Depression program.

On February 11, 2003, the Division issued a Pediatric Written Request for SEROQUEL Tablets (NDA 20-639) for the treatment of schizophrenia and bipolar mania. AstraZeneca is currently working to fulfill the Written Request through the conduct of an ongoing pediatric clinical development program. (b) (4)

(b) (4)

(b) (4)

DEBARMENT CERTIFICATION

Re: **NDA 22-047**

SEROQUEL® SR (quetiapine fumarate sustained-release) Tablets

Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP (AstraZeneca), that we did not use and will not use in connection with this New Drug Application for SEROQUEL® SR Tablets, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

Anthony Rogers, Vice President
Regulatory Affairs
AstraZeneca

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-047

AstraZeneca Pharmaceuticals LP
Attention: Gerald L. Limp
Manager, Marketed Products Group
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850

Dear Mr. Limp:

Please refer to your July 17, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel SR (quetiapine fumarate) 50mg, 200mg, 300mg, and 400mg sustained-release tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 25, 2007. The purpose of the meeting was to discuss your proposed responses to the Chemistry, Manufacturing and Controls (CMC) Information Request Letter dated March 30, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.
If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager for Quality, at (301) 796-2055.

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

Enclosure

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

Sponsor Name:	AstraZeneca
Application Number:	NDA 22-047
Product Name:	Seroquel SR (quetiapine fumarate)
Meeting Requestor:	Ramesh Sood, Ph.D., ONDQA
Meeting Type:	Type A
Meeting Category:	CMC Guidance Meeting
Meeting Date and Time:	April 25, 2007, 1200 – 1300 ET
Meeting Location:	Teleconference
Received Briefing Package	April 16, 2007
Meeting Chair:	Ramesh Sood, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES:

Division of Pre-Marketing Assessment I

Ramesh Sood, Ph.D.; Branch Chief
Thomas F. Oliver, Ph.D.; Pharmaceutical Assessment Lead
Prafull Shiromani, Ph.D.; Review Chemist (MM Rev: May 23, 2007)
Wendy Wilson, Ph.D.; Review Chemist (MM Rev: May 22, 2007)
Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

EXTERNAL ATTENDEES:

Norbert Ealer; Regulatory CMC
Paul Stott; Pharmaceutical Analytical Research and Development (PAR&D)
Daniel Brown; PAR&D
Mike Koenigbauer; Analytical Development
Husheng Yang; Analytical Development

1.0 BACKGROUND

AstraZeneca (AZ) has submitted NDA 22-047 for Seroquel SR (quetiapine fumarate) 50 mg, 200 mg, 300 mg, and 400 mg extended release tablets, proposed for the treatment of schizophrenia. On March 30, 2007, a Chemistry, Manufacturing and Controls (CMC) Information Request (IR) letter was sent to Gerald Limp, Director, Regulatory Affairs for AstraZeneca, containing several outstanding CMC issues. To facilitate the response, a teleconference was offered to Norbert Ealer of AstraZeneca by Ramesh Sood, Ph.D. Branch Chief in the Office of New Drug Quality Assessment (ONDQA) through Scott N. Goldie, Ph.D. Regulatory Health Project Manager for Quality, ONDQA on March 30, 2007. After reviewing the IR letter, AstraZeneca formally requested a Type A CMC Guidance meeting on April 13, 2007, received April 16, 2007 to discuss AstraZeneca's proposed responses to FDA's IR letter. The meeting was granted on April 16, 2007, by Scott N. Goldie, Ph.D. The briefing package that provided additional information in the form of PowerPoint slides to facilitate discussion regarding AstraZeneca's proposed responses was included in the Type A meeting request and referred to during the meeting by the participants. The teleconference occurred on April 25, 2007, and the discussion is captured below. The specific contents of each of the points are included for clarity, using the same numbering system as in the March 30, 2007 IR letter.

2.0 DISCUSSION

2.1 Multivariate Model – ANN

2.1.1 Information Request 1a. Describe how changes to the ANN model (e.g., changing excipient ratios, addition/ removal/changing input variables, model modification due to numerous batch failures, new ANN model/software) would be reported to the Agency. Delineate your plan to manufacture product in the event the model is unavailable.

Meeting Discussion: AstraZeneca referred to Slide 4 and Slide 5 during the meeting discussion. (b) (4)

2.1.2 Information Request 1b. Since you have seen higher instances of dissolution prediction and actual results disagreements for the 50 mg tablets, describe your plans to refine the ANN model for the 50 mg tablet strength. Describe any (b) (4) specification restrictions that limit the material properties to those used for the training data set.

Meeting Discussion: AstraZeneca referred to Slide 6 during the discussion.

AstraZeneca committed to provide the batch information and (b) (4) for the added 50 mg batches used to retrain the ANN. (b) (4)

2.1.3 (b) (4)

Meeting Discussion: AstraZeneca referred to Slide 7 during the discussion. FDA agreed that AstraZeneca's response as proposed in the slide was adequate. No further discussion occurred during the meeting.

2.1.4 Information Request 1d. Justify excluding the 1, 2, 4, 16, and 20 hour dissolution time points from model verification activities. Provide model verification results for the 1, 2, 4, 16, and 20 hour dissolution time points, if available.

Meeting Discussion: AstraZeneca referred to Slide 8 during the discussion. FDA agreed that AstraZeneca's response as proposed in the slide was adequate. No further discussion occurred during the meeting.

2.1.5 Information Request 1e. Define the frequency of ANN model periodic reviews described in the quality management plan (see IR response to Question 3d dated January 29, 2007).

Meeting Discussion: AstraZeneca referred to Slide 9 during the discussion. AstraZeneca committed to propose frequencies of batches that would trigger review of the ANN.

2.1.6 Information Request 1f. Define how you plan to accommodate the impact of personnel turnover and personnel training on the ANN model.

Meeting Discussion: AstraZeneca referred to Slide 10 during the discussion. FDA agreed that AstraZeneca's response as proposed in the slide was adequate. No further discussion occurred during the meeting.

2.1.7 Information Request 1g. Define how changes to analytical methods that support the ANN model, such as the (b) (4) content NMR method and dissolution method, impact the predictive capabilities of the ANN model.

Meeting Discussion: AstraZeneca referred to Slide 11 during the discussion. FDA agreed that AstraZeneca's response as proposed in the slide was adequate. No further discussion occurred during the meeting.

2.1.8 Information Request 1h. Describe your plans to incorporate knowledge learned from stability results in the ANN model.

Meeting Discussion: AstraZeneca referred to Slide 12 during the discussion. AstraZeneca committed to provide a contingency plan if stability results begin to show time dependent trends or significant changes in dissolution behavior.

2.1.9 Information Request 1i. Detail the sensitivity of the ANN model to dissolution testing sample number. Describe how the ANN model differentiates the stage of dissolution testing (S1, S2 or S3).

Meeting Discussion: AstraZeneca referred to Slide 13 during the discussion. AstraZeneca committed to incorporate responses to the issues raised in the information request letter. AstraZeneca stated that the ANN was to be used to predicts pass or failure of batches based on dissolution performance but not to identify trends toward dissolution failure.

2.2 Information Request 2. Describe how the drug product stability data generated for the 50, 200, 300, 400 mg primary NDA stability batches is predictive of product stability for the other ratios (b) (4) over your proposed expiry.

Meeting Discussion: AstraZeneca referred to Slide 14 during the discussion. AstraZeneca committed to provide all available stability data of additional Seroquel SR batches with (b) (4) by April 30, 2007, requesting that additional data submission not impact the review clock, which FDA agreed to.

2.3 Information Request 3. Regarding your response to FDA's 'magnesium stearate' question, dated 25 January 2007: your new data is based on tablets manufactured using a (b) (4). However, our original question remains unanswered, viz. provide information that shows how simultaneous changes, within the proposed limits, in the levels of (b) (4) and magnesium stearate concentrations would affect drug release and other parameters.

Meeting Discussion: AstraZeneca referred to Slide 15 and Slide 16 during the discussion. AstraZeneca committed to provide data upon completion of their DoE to evaluate simultaneous changes of (b) (4) and magnesium stearate level for 50 mg and 400 mg tablet strength submit all data as a 'Post-Approval Supplement', in accordance with SUPAC MR Guidance. AstraZeneca concluded that any changes to magnesium stearate will be processed in accordance with SUPAC guidance.

2.4 Information Request 4. (b) (4)

Meeting Discussion: AstraZeneca referred to Slide 17 during the discussion. FDA agreed that AstraZeneca's response as proposed in the slide was adequate, and acknowledged that the particle size measurement described in the table are measured using different methods.

2.5 Information Request 5. Clarify the inconsistency between your statement, 'the test for Degradation products by HPLC will not be applied at the time of manufacture in P.5.6-Justification of Specification for Drug Product' and the 'Specification for Drug Product' table (P.5.1) wherein one of the test procedures is 'Degradation products by HPLC'.

2.5.1 Information Request 5a. We recommend that this test should be performed at release for all batches, not only the annual stability batch.

Meeting Discussion: AstraZeneca referred to Slide 18 during the discussion. FDA reiterated that the 'Test for Degradation Products' should be applied at release for all batches and not just the annual stability batch.

Section 2.7 of ICH Quality Guideline Q6A states that: 'for the tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic'. The guideline does not eliminate the test. AstraZeneca committed to provide justification for testing of degradation products in future submission.

2.6 Information Request 6. Provide justification for proposing 36 month shelf life based on 12 months stability data for 50 mg and 400 mg strengths – ref. P.8.1 Stability Summary and Conclusions for Drug Product.

Meeting Discussion: AstraZeneca referred to Slide 19 during the discussion. AstraZeneca committed to provide full data sets of the 24 months stability data for the 50 mg and 400 mg strengths: FDA committed that submission of this latest stability data for review will not impact the review clock provided that the data is received by ONDQA by 30-APR-2007.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

AstraZeneca committed to incorporate FDA's suggestions and comments into their submission, and further committed to submit the information identified in the meeting discussion section by 30-APR-2007. FDA committed to not modify the review clock provided that the data described in the meeting discussion section is complete and received by 30-APR-2007.

5.0 CONCURRENCE:

{See appended electronic signature page}

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

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

6.0 ATTACHMENTS AND HANDOUTS

The following slides were submitted prior to the meeting by AstraZeneca to use as the basis of the discussion at the teleconference on April 25, 2007. The slides were first emailed to Scott N. Goldie, Ph.D. on April 13, 2007 and submitted to the administrative file on April 16, 2007 as part of a Type A meeting request.

Slide 1

Seroquel SR
(Quetiapine fumarate)

Proposed Responses to Questions Received on March 30, 2007 Relating to NDA 22-047

Meeting date: April 25, 2007

1 AstraZeneca

9 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/ TS)

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

/s/

Scott Goldie
5/23/2007 11:47:33 AM

Ramesh Sood
5/23/2007 01:39:38 PM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 22-047	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type: NA	
Proprietary Name: Seroquel XR Established Name: quetiapine fumarate Dosage Form: Extended-Release Tablets		Applicant: AstraZeneca	
RPM: Kimberly Updegraff		Division: 130	Phone # 301-796-2201

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 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)): Provide a brief explanation of how this product is different from the listed drug. ☐ 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.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	May 17, 2007
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None First Cycle
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☐ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ **(**iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ 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	☐ Yes ☐ No

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

within the 45-day period). *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*).* *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.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	4/24/07 Clinical Team Leader
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	X
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	X
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	NA
• Original applicant-proposed labeling	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	NA
• Original applicant-proposed labeling	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	X
• Most recent applicant-proposed labeling	X
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS ☐ DSRCS ☐ DDMAC ☒ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	9/9/06 Filing Review
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ 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. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	Yes
• Incoming submission documenting commitment	X
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
❖ Internal memoranda, telecons, email, etc.	X
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	None
• Pre-NDA/BLA meeting *(indicate date)*	6/20/03 ; 10/13/05 (cancelled per sponsor request)
• EOP2 meeting *(indicate date)*	☐ No mtg 5/13/05
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	4/25/07 ; 5/9/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☒ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☒ Review & FONSI *(indicate date of review)*	1/19/07
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☒ Acceptable 4/3/07 ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation ❖ Per Tom Oliver, this is now done in the review, no longer sent out on a regular basis.	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Memo – 4/16/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	X
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	X
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 4/2/07
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 5/10/07

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.

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/s/

Kimberly Updegraff
5/22/2007 11:53:31 AM

Updegraff, Kimberly

From: Limp, Gerald L [gerald.limp@astrazeneca.com]
Sent: Tuesday, May 15, 2007 1:52 PM
To: Updegraff, Kimberly
Subject: RE: NDA 22-047 ; Seroquel XR Phase 4 Commitment
Follow Up Flag: Follow up
Flag Status: Completed

AstraZeneca accepts the phase 4 obligation as noted below, for NDA 22-047.

Gerald Limp
Regulatory Affairs Director
AstraZeneca Pharmaceuticals

-----Original Message-----
From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Tuesday, May 15, 2007 12:53 PM
To: Limp, Gerald L
Subject: NDA 22-047 ; Seroquel XR Phase 4 Commitment

Hi Gerald,

We need your agreement to the following Phase 4 Postmarketing Commitment for Seroquel XR.

3. You will conduct studies to investigate dose-dumping in the presence of alcohol. You will perform dissolution studies for all Seroquel XR strengths using the accepted dissolution conditions with the addition of 0%, 5%, 20%, and 40% of ethanol to the dissolution media. You will submit a final report on or before August 31, 2007.

The wording is changed in this version, please disregard the previous version of commitment #3.

Thank you,
Kim Updegraff
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Phone: (301)796-2201

Updegraff, Kimberly

From: Limp, Gerald L [gerald.limp@astrazeneca.com]
Sent: Monday, May 14, 2007 6:14 PM
To: Updegraff, Kimberly
Subject: RE: Seroquel XR 22-047
Follow Up Flag: Follow up
Flag Status: Completed

AstraZeneca Pharmaceuticals agrees to the phase 4 commitments as listed below for NDA 22-047.

Gerald Limp
Regulatory Affairs Director
AstraZeneca Pharmaceuticals
Wilmington, DE

-----Original Message-----
From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Monday, May 14, 2007 9:16 AM
To: Limp, Gerald L
Subject: Seroquel XR 22-047

Dear Gerald,

We need your agreement to the following Phase 4 Postmarketing Commitments for Seroquel XR (22-047):

1. You will assess the safety and effectiveness of quetiapine fumarate (as either the immediate release or the extended release formulation) as a treatment for schizophrenia in pediatric patients ages 13 to 17 on or before October 30, 2011.

2. The tablet intagliation will be modified to XR plus dosage strength which addresses the preference of DMETS that the intagliation more closely resemble the proprietary name modifier. This will be filed as a CMC CBE-30 supplement on or before October 30, 2007.

Please let me know if you have any questions.

Sincerely,

Kimberly Updegraff
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Phone: (301)796-2201

Updegraff, Kimberly

From: Updegraff, Kimberly
Sent: Wednesday, March 28, 2007 3:53 PM
To: Limp, Gerald L
Cc: Updegraff, Kimberly
Subject: Seroquel (22-047) DMETS comments

Dear Gerald,

I have attached comments from DMETS concerning the questions posed in your email dated March 15, 2007 (see below).

Question: Within the section that provides comments from DMETS, there is a comment that we modify our tablet intagliation. Is this their preference, a recommendation, or a requirement?
DMETS Response : Preference. The intagliation of the tablet with the modifier and strength was proposed by the Sponsor as a measure to help ensure differentiation of the extended- and immediate- release formulations in the marketplace. DMETS acknowledges that the intagliation of the tablet requires modification from " SR " to " XR", but believes that this marking represents an important safety measure. DMETS has also noted that mix-ups between Seroquel and Seroquel XR are likely to occur, and that the collective measures proposed by the Sponsor to ensure product differentiation are necessary to help to minimize these potential errors. As such, DMETS would strongly prefer that the Sponsor maintain this commitment.

Question: We already have tooling to produce tablets with the intagliation that is referenced within the NDA; this would require an additional investment of funds and time if this change is a requirement. If it is a requirement, can that be implemented as a post-approval commitment?
DMETS Response : The Sponsor notes that they have tools to produce tablets intagliated with "SR" (the previously proposed modifier) and the strength. DMETS acknowledges that the intagliation of the tablets with "XR" and strength may require an additional investment of funds and time, but believes that the efforts would be worthwhile. DMETS is not completely opposed to implementing this change as a post-approval commitment, though DMETS would prefer that the Sponsor meet this commitment prior to marketing the product for the following reasons:
1. DMETS is concerned that the launch of Seroquel XR will not have this safety measure in place, which might prevent errors of administration in the outpatient and inpatient setting. Although the intagliation of the tablet with " XR " will not prevent mix-ups between Seroquel and Seroquel XR, DMETS believes that it could help detect errors prior to administration by providing a visual means for patients and caregivers to readily identify the product formulation at the point of administration.
2. DMETS has concern that the change in tablet appearance in the post- marketing phase introduces a new source of confusion to the product line.

1. In an outpatient setting, tablet appearance and markings are routinely used by pharmacists and computer software programs in the final verification step when dispensing he product. Changing the markings post-approval would require some means of updating the software programs, and possibly alerting pharmacists to this change. This process could be complicated by the fact, that for some length of time, the markings on the Seroquel XR tablets could vary based on the date of manufacture.
2. Patients using Seroquel XR may become accustomed to the appearance and markings of the tablet at launch. Subsequent changes to the tablet appearance may be confusing and disconcerting to the patient population. If the Sponsor has just cause for not meeting this commitment prior to marketing the product, DMETS requests that they provide the Agency with the following information:

- 1) If the requirement is met as a post-approval commitment, would the tablets be intagliated with any information in the interim? If so, please specify in detail. DMETS is concerned that the Sponsor may proceed to intagliate the tablets with the old modifier (SR) and strength which would discordant

with the proprietary name (Seroquel XR) and be a source of confusion.

- 2) When providing an expected timeline of implementation, please provide detail regarding the length of time required to achieve this change in manufacturing, along with the projected time to deplete the initial supply and the projected duration of overlap between the two tablets appearance.
- 3) Please indicate any additional measures that could be employed to minimize confusion resulting from this change in the post-marketing phase.

Question: Lastly, we are investigating ways to assure the 22-047 tablets are perceived to be different from the 20-639 immediate release tablets, and to improve the match between the XR trade name and drug name. Would the FDA agree with a change from 'quetiapine fumarate sustained release' to 'quetiapine fumarate extended release' tablets, which is a phrase DMETS use within their comments. It is our understanding that no technical aspects for tablet manufacture or drug release characteristics are represented by either concept, and they are basically equivalent in meaning.
DMETS Response : DMETS does not believe that relying on the Sponsor 's "understanding" is prudent regarding the nomenclature of the proposed formulation. The Sponsor 's assumption that the sustained- and extended-release terms are "basically equivalent in meaning" is presumptuous; "extended-release" is a recognized dosage form in the United States Pharmacopeia while "sustained- release" is not. In DMETS' s opinion, this matter should be resolved by consulting Richard Lostritto of the CDER Labeling and Nomenclature Committee (LNC) on the proper designation of the established name for the modified-release product.

Question: If the FDA agrees with this change, how do we initiate this? Would this be a change we would include in our updated draft label?
DMETS Response : We do not agree with this revision. So we have no further comments to offer.

Please let me know if you have any questions or concerns.

Sincerely,

Kimberly Updegraff,B.S.,R.Ph.,M.S.
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation
Phone: (301)796-2201
Fax: (301)796-9838
Email: Kimberly.Updegraff@fda hhs.gov

From: Limp, Gerald L [mailto:gerald.limp@astrazeneca.com]
Sent: Thursday, March 15, 2007 10:51 AM
To: Updegraff, Kimberly
Subject: RE: Seroquel (22-047)

Thanks, Kim, for progressing this correspondence. Our team is currently reworking the draft label to address the comments from SEALD. We will respond within the timeline you provide within the letter.

Within the section that provides comments from DMETS, there is a comment that we modify our tablet intagliation. Is this their preference, a recommendation, or a requirement? We already have tooling to produce tablets with the intagliation that is referenced within the NDA; this would require an additional investment of funds and time if this change is a requirement. If it is a requirement, can that be

implemented as a post-approval commitment?

Lastly, we are investigating ways to assure the 22-047 tablets are perceived to be different from the 20-639 immediate release tablets, and to improve the match between the XR trade name and drug name. Would the FDA agree with a change from 'quetiapine fumarate sustained release' to 'quetiapine fumarate extended release' tablets, which is a phrase DMETS use within their comments. It is our understanding that no technical aspects for tablet manufacture or drug release characteristics are represented by either concept, and they are basically equivalent in meaning. If the FDA agrees with this change, how do we initiate this? Would this be a change we would include in our updated draft label?

Thanks in advance,

Gerald Limp
AstraZeneca Pharmaceuticals
302-886-8017

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

/s/

Kimberly Updegraff
4/2/2007 01:45:05 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-047

AstraZeneca Pharmaceuticals LP
Attention: Gerald L. Limp
Manager, Marketed Products Group
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850

Dear Mr. Limp:

Please refer to your July 17, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel SR (quetiapine fumarate) 50mg, 200mg, 300mg, and 400mg sustained-release tablets.

We also refer to your submissions dated August 30, 2006 and September 19, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request that you respond in written form as soon as possible so that the information can be reviewed prior to the PDUFA action date for your application of May 17, 2007:

1. Multivariate Model – ANN
    a. Describe how changes to the ANN model (e.g., changing excipient ratios, addition/ removal/changing input variables, model modification due to numerous batch failures, new ANN model/software) would be reported to the Agency. Delineate your plan to manufacture product in the event the model is unavailable.
    b. Since you have seen higher instances of dissolution prediction and actual results disagreements for the 50 mg tablets, describe your plans to refine the ANN model for the 50 mg tablet strength. Describe any (b) (4) specification restrictions that limit the material properties to those used for the training data set.
    c. (b) (4)

d. Justify excluding the 1, 2, 4, 16, and 20 hour dissolution time points from model verification activities. Provide model verification results for the 1, 2, 4, 16, and 20 hour dissolution time points, if available.

e. Define the frequency of ANN model periodic reviews described in the quality management plan (see IR response to Question 3d dated January 29, 2007).

f. Define how you plan to accommodate the impact of personnel turnover and personnel training on the ANN model.

g. Define how changes to analytical methods that support the ANN model, such as the (b) (4) content NMR method and dissolution method, impact the predictive capabilities of the ANN model.

h. Describe your plans to incorporate knowledge learned from stability results in the ANN model.

i. Detail the sensitivity of the ANN model to dissolution testing sample number. Describe how the ANN model differentiates the stage of dissolution testing (S1, S2 or S3).

2. Describe how the drug product stability data generated for the 50, 200, 300, 400 mg primary NDA stability batches is predictive of product stability for the other ratios (b) (4) over your proposed expiry.

3. Regarding your response to FDA's 'magnesium stearate' question, dated 25 January 2007: your new data is based on tablets manufactured using a (b) (4). However, our original question remains unanswered, viz. provide information that shows how simultaneous changes, within the proposed limits, in the levels of (b) (4) and magnesium stearate concentrations would affect drug release and other parameters.

4. (b) (4)

5. Clarify the inconsistency between your statement, 'the test for Degradation products by HPLC will not be applied at the time of manufacture in P.5.6-Justification of Specification for Drug Product' and the 'Specification for Drug Product' table (P.5.1) wherein one of the test procedures is 'Degradation products by HPLC'.
   a. We recommend that this test should be performed at release for all batches, not only the annual stability batch.

6. Provide justification for proposing 36 month shelf life based on 12 months stability data for 50 mg and 400 mg strengths – ref. P.8.1 Stability Summary and Conclusions for Drug Product.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager for Quality, at (301) 796-2055.

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

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

/s/

Ramesh Sood

3/30/2007 01:50:04 PM

NDA 22-047

AstraZeneca Pharmaceuticals LP
Attention: Gerald L. Limp
Manager, Marketed Products Group
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850

Dear Mr. Limp:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumerate) sustained-release 50mg, 200mg, 300mg, and 400mg tablets.

The Division of Medication and Technical Support (DMETS) and the Division of Psychiatry Products have the following recommendations/comments concerning packaging and labeling:

A. CONTAINER LABEL

1. Container Closure

a) The immediate-release Seroquel product line utilizes a blue container closure on all of the retail bottles and bulk bottles (1000 count) of 25 mg and 50 mg tablets.

You have proposed using a [redacted] (b) (4)

[redacted] (b) (4)

DMETS believes that Seroquel SR and Seroquel have an

increased risk for selection errors because of the similar nomenclature of the products, overlapping strengths, net quantity of containers, primary container label's color scheme.

Therefore, DMETS recommends that you utilize white container closures for the Seroquel SR product line to help lessen the potential for product selection errors with Seroquel SR and Seroquel.

b) DMETS also noted that the Seroquel SR product line is packaged in "unit of use quantities" of 60 tablets. DMETS recommends that you employ Child Resistant Closures for all strengths of Seroquel SR tablets in the 60 count bottles.

The use of Child Resistant Closures would increase the pharmacist's opportunity to directly label and dispense the manufacturers' stock bottle. From a medication errors perspective, this may have several benefits. Direct labeling of the pharmacy container decreases the number of steps in the dispensing process, which inherently decreases the opportunity for error. Since there are multiple opportunities for the Seroquel SR to be confused with Seroquel throughout the medication use process, minimizing the number of opportunities could help improve the safe use of the product. Direct labeling of the manufacturer stock bottle ensures that the pharmacist has the original container at the point of final verification, thus enhancing the likelihood to catch product selection errors. Lastly, direct labeling of the manufacturer bottle gives patients the opportunity to verify the contents, and potential identify errors prior to ingestion.

2. Container Label

a) DMETS is concerned that the proposed color scheme for the Seroquel SR may increase the potential for selection errors and confusion with the Seroquel product line. (b) (4)

DMETS recommends that you employ a different color for Seroquel SR container labels that does not overlap with the Seroquel product line, in order to help minimize the potential for selection errors.

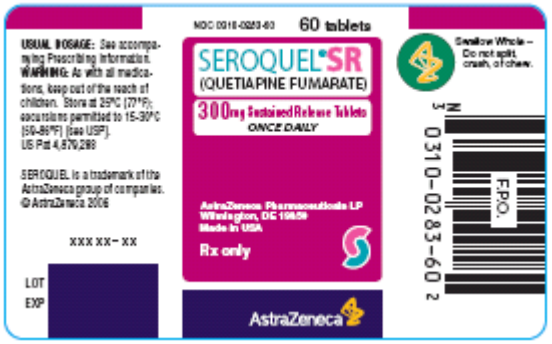
Table 1. Proposed Seroquel SR container labels and Seroquel container labels

b) DMETS is concerned that the proposed color scheme for the 300 mg strength of Seroquel SR may lead to selection errors. For the 300 mg strength of Seroquel SR, the sponsor has proposed using a (b) (4)

[redacted]

DMETS recommends that you employ a different color for Seroquel SR container labels that does not overlap with the Seroquel product line, in order to help minimize the potential for selection errors.

Table 2. Proposed container label for Seroquel SR 300mg compared to Seroquel 25 and 300 mg

c) DMETS recommends the established dosage form (extended-release tablets) follow the established name, and not the strength of the product as proposed. In addition, DMETS recommends that the dosage form be displayed in black.

d) Normally, DMETS would recommend displaying the root name (i.e. "Seroquel") and established name (i.e. "Quetiapine Fumarate") using upper and lower case letters, since the use of all capitalized letters decreases the readability of information. However, in this instance, DMETS does not object to the use of all capitalized letters for the proprietary name (i.e. SEROQUEL SR), since this may help to differentiate the product from Seroquel. DMETS does recommend that you use upper and lower case letters for the established name, to improve readability.

e) DMETS recommends you increase the size and prominence of "ONCE DAILY" on the primary display panel. DMETS also recommends that you reference the "Once daily" dosage frequency of the product on the secondary display panel under "USUAL DOSAGE" to reinforce this message.

f) Remove the (b) (4) graphic from the primary display panel from all strengths of the Seroquel SR product line. (b) (4)

(b) (4)
[redacted]

g) DMETS recommends that you display the strength and dosage form in colors that provide good visual contrast to increase readability and prominence of this information. (b) (4)
[redacted]

B. PROFESSIONAL SAMPLES

1. Carton Label
   a) See CONTAINER LABEL comments 2a, 2b, 2c, 2d, 2e, 2f, 2g.

2. Container Label
   a) See CONTAINER LABEL comments 2a, 2b, 2c, 2d, 2e, 2f, 2g.

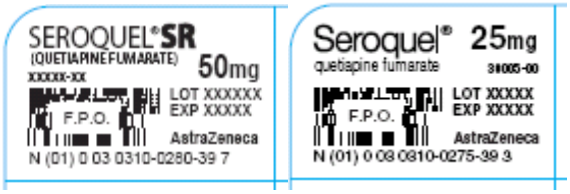
   b) Include a descriptor to indicate how the product should be dosed (e.g. "Once-A-Day Dosing") on the primary display panel of the Seroquel SR container bottle label for the samples. DMETS believes that this statement may, to some degree, lessen confusion with the existing Seroquel products.

C. HOSPTIAL UNIT-DOSE

1. Unit-dose blister Label

   a) GENERAL COMMENTS

   The labels used for the unit-dose Seroquel SR appear very similar to Seroquel and may increase confusion between the products if both are stocked within an institution (see images below).



   The similar appearance of the labels could lead to product confusion when stocking, dispensing, and administering the products. DMETS recommends that you explore different layouts and formats to improve differentiation of these products.

If you are unable to pursue alternative formats, DMETS believes that mix-ups are likely to occur in facilities that stock both products. To help minimize the potential for confusion, DMETS recommends the following to improve the safety of the current proposed labels:

1) The dosage form ("extended-release tablets") is missing. Add the dosage form to the label after the established name.

2) Normally, DMETS would recommend displaying the root name (i.e. "Seroquel") and established name (i.e. "Quetiapine Fumarate") using upper and lower case letters, since the use of all capitalized letters decreases the readability of information. However, in this instance, DMETS does not object to the use of all capitalized letters for the proprietary name (i.e. SEROQUEL SR), since this may help to differentiate the product from Seroquel. DMETS does recommend that you use upper and lower case letters for the established name, to improve readability. Additionally, if the unit-dose label has adequate space, DMETS recommends increasing the size of the type used to display the established name and dosage form to further improve the readability of the established name and dosage form, as this information may be used frequently as the primary product identifier in an inpatient settings.

3) Consider displaying the Proprietary Name in reverse block print, maintaining bolded "SR" (see sample below). Although bolded, the barcode on the label decreases the prominence of the SR modifier, which could lead to errors.

SEROQUEL **SR**

4) DMETS recommends that the placement of the strength be left justified. The proposed placement decreases the prominence of the strength, and DMETS has concern that it could lead to confusion between the various strengths of Seroquel SR.

5) Left-justify the Lot and Expiration, and Manufacturer information, and mover the barcode to the right. DMETS believes that this will improve the overall readability of the information, and help to provide some differentiation from the immediate-release unit dose Seroquel tablets.

2. Carton Label

a) See CONTAINER LABEL comments 2a, 2b, 2c, 2d, 2e, and 2f.

b) Remove the (b) (4) graphic from the primary display panel from all strengths of the Seroquel SR product line. (b) (4)

c) Include a descriptor to indicate how the product should be dosed (e.g. "Once-A-Day) Dosing" on the primary display panel of the Seroquel SR product line. DMETS believes that this statement may, to some degree, lessen confusion with the existing Seroquel products.

D. PRESCRIBING INFORMATION

1. Dosage and Administration

a) (b) (4)

Please respond and submit revised labeling pertaining to the above comments and requests within 30 days from the date of this letter in order to allow the Agency sufficient time to complete our reviews within the goal date timeframe of this application (May 17, 2007). If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
3/19/2007 12:18:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-047

AstraZeneca Pharmaceuticals LP
Attention: Gerald L. Limp
Manager, Marketed Products Group
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850

Dear Mr. Limp:

Please refer to your New Drug Application (NDA) dated and received July 17, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) sustained-release 50 mg, 200 mg, 300 mg, and 400 mg tablets.

Below are comments and requests from the Study Endpoints and Label Development (SEALD) Team concerning your proposed PLR labeling for Seroquel (NDA 22-047) as well as comments from the Division of Medication Errors and Technical Support (DMETS) concerning your proposed trade name.

SEALD Comments

HIGHLIGHTS:

- The Highlights section must be limited in length to one-half page, in 8 point type, two-column format [See 21 CFR 201.57(d)(6) and (d)(8)]. If this is not possible, please submit a formal waiver.

- The "Initial US. Approval: pending" statement should not be in all capital letters. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Revise the Boxed Warning so that the title is in all capital letters. The required statement ***See full prescribing information for complete boxed warning*** should appear immediately after the title. Add cross-references to each bulleted statement. The Boxed Warning should read:

  WARNING: MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA
  See full prescribing information for complete boxed warning.

- **Atypical antipsychotic drugs may rarely lead to an increased risk of death (add cross-reference)**
- **Causes of death are variable (add cross-reference)**
- **Quetiapine is not approved for elderly patients with Dementia- Related Psychoses (add cross-reference).**

[See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Since there are no recent major changes, please delete this section heading. [See 21 CFR 201.56(d)(4)].

- Add a cross-reference after the bullet under Indications and Usage. [See 21 CFR 201.56(d)(3)]

- Create bulleted statements under Dosage and Administration and include cross- references for all statements. [See 21 CFR 201.56(d)(3)]

- Under Adverse Reactions, your proposed required statement currently reads:

  To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch for (b) (4)

  The AstraZeneca phone number must connect callers directly to a location for voluntary reporting of adverse events. A general phone number that is not specifically designated for adverse event reporting should not be included. (b) (4) should be deleted since it is not included in the required statement. [See 21 CFR 201.57(a)(11)]

- Add "Revised:" before the month/year after the required statement **"See 17 for PATIENT COUNSELING INFORMATION".** [See 21 CFR 201.57(a)(15)]

FULL PRESCRIBING INFORMATION: CONTENTS

- Add an asterisk and use all capital letters for the title **"Full Prescribing Information: Contents".**
  [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Limit contents to one-half page in length, in 8 point type, two-column format. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Unbold the section subheadings. Only section headings should be bolded. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Section and subsection headings can only be numbered. Do not number headings within a subsection (e.g. 2.3.1 Maintenance Treatment). Use headings without numbering (e.g., *Maintenance Treatment*). Please correct in Highlights, Contents and the FPI. [See 21 CFR 201.5(c)]

- The required subsections under 9 Drug Abuse and Dependence are named the following:

    9.1 Controlled Substance
    9.2. Abuse
    9.3 Dependence

Please revise in both Contents and the FPI. [See CFR 201.57(c)(10)]

- Add the required footnote "*Sections or subsections omitted from the full prescribing information are not listed" at the end of Contents.
  [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

FULL PRESCRIBING INFORMATION

- Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use bold print or capitalize the section headings in cross-references. For example, [*see Clinical Pharmacology (12)*], not [see **CLINICAL PHARMACOLOGY** (12)]. Please fix your cross-references throughout the FPI. [Implementation Guidance]

- Under Adverse Reactions, you refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise your Adverse Reactions section accordingly.

DMETS Comments

- DMETS remains unconvinced that SR is an appropriate modifier for the product, and thus maintains that the proprietary name, Seroquel SR, should not be used.

- DMETS concludes that the XR modifier is an acceptable choice for the proposed product, and does not object to the use of the proprietary name, Seroquel XR.

- DMETS believes that it is likely that errors will occur as a result of Seroquel and Seroquel XR confusion. DMETS believes that the risks inherent to the use of a modifier for this

product line extension should be addressed by the actions proposed in your submissions dated November 30, 2006 and December 19, 2005 including: actions to educate health care practitioners about the differences between immediate- and the extended-release formulation of Seroquel; the use of a "Once-A-Day-Dosing" descriptor on package labels, the intagliation of the Seroquel XR tablets with ' XR ' and strength.

Please respond and submit revised labeling pertaining to the above comments and requests within 30 days from the date of this letter in order to allow the Agency sufficient time to complete our reviews within the goal date timeframe of this application (May 17, 2007).

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
3/13/2007 04:36:30 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-047

AstraZeneca Pharmaceuticals LP
Attention: Gerald L. Limp
Manager, Marketed Products Group
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850

Dear Mr. Limp:

Please refer to your July 17, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel SR (quetiapine fumarate) 50mg, 200mg, 300mg, and 400mg sustained-release tablets.

We also refer to your submissions dated August 30, 2006 and September 19, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section 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:

a) You have stated that the amount of magnesium stearate may (b) (4)

b) Identify which blister pack configuration (b) (4) will be marketed.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager for Quality, at (301) 796-2055.

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

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/s/

Ramesh Sood

12/21/2006 12:03:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-047

AstraZeneca Pharmaceuticals LP
Attention: Gerald L. Limp
Manager, Marketed Products Group
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850

Dear Mr. Limp:

Please refer to your July 17, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel SR (quetiapine fumarate) 50mg, 200mg, 300mg, and 400mg sustained-release tablets.

We also refer to your submissions dated July 17, 2006, August 30, 2006 and September 19, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section 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. C2.3.P.2.2 Addendum C – SEROQUEL SR formulations:
   a) Study 1: Provide a summary of the statistical analysis (i.e. mathematical model, values of correlation and regression coefficients, standard error, etc.) employed in this Plackett Burman design.
   b) Study 2:
      i) Provide the physical units corresponding to the 'Low' and 'High' qualitative units presented in the Plackett Burman design.
      ii) Provide a summary of the statistical analysis (i.e. mathematical model, values of correlation and regression coefficients, standard error, etc.) employed in this DOE.
      iii) Substantiate your conclusion that the combined effect of (b) (4)

c) Stage 3 – Multivariate relationship-Surface Response Experimental Design:
   i) Provide a summary of the statistical analysis (i.e. mathematical model, values of correlation and regression coefficients, standard error, etc.) employed in this design.
   ii) Quantify the map of dissolution performance – Figure C14 – and describe the optimal formulation for each strength (b) (4) of the product.
   iii) Provide an assessment of the prediction power of this model using the (b) (4) characteristics and ratios used in the primary NDA stability batches for all strengths.
   iv) Based on the above designs provide Contour or Response Surface Plots with (b) (4) content of the (b) (4) and magnesium stearate, respectively, as independent variables and the dissolution profile as the dependent variable of interest, (The use of contour diagrams allows visual understanding of the significance of the regression equations by demonstrating the contribution of variables, as well as their interactions and curvature effects, to the measured responses. Contour diagrams also graphically depict maxima and minima in the response surface).

2. Appendix E – Multivariate Model

a) Describe the rationale for the exclusion of batch size as an input variable in the ANN.

b) Clarify whether the 24 commercial scale batches were or were not part of the 177 batches that were used to train the network. Also, clarify whether or not the primary NDA stability batches were included in either the training or validation sets. Provide the mathematical model developed by the ANN, if possible.

c) Provide an assessment of the prediction power of this model using the (b) (4) characteristics and ratios used in the primary NDA stability batches for all strengths.

d) Describe the method used to optimize the ANN architecture.

e) Describe how the magnitude of the error in the measured response data (dissolution data) compares to the ANN model error.

f) Provide the RMSEP for the training set (N=177) at 6 hours and 12 hours. Provide the maximum and average RMSECV at 6 hours and 12 hours.

g) Clarify why the RMSEP was calculated using only actual and/or predicted dissolution profiles that met the dissolution acceptance criteria. Identify the batches that were excluded and provide the specification time points that failed for each batch.

h) Subset the training set data based on tablet strength and batch size and provide the RMSEP at 6 hours and 12 hours for each subset.

i) Provide the electronic spreadsheet and summary table of all input parameters, predicted model outputs and actual response data for the 24 verification batches.

3. Final Model:

   a) Clarify which model will be used for determining the [redacted] (b) (4) during routine commercial manufacture.

   b) Provide a comparison of the prediction power of the two models (Surface Response and NN).

   c) Describe how the use of the model is incorporated into your quality system.

   d) Outline the plan for maintaining and updating the model addressing use for both normal operations and dissolution failures.

4. Labeling

   a) The established name in the labeling is represented as "Quetiapine fumarate" whereas the strength is based on the parent base. The strength should be consistent with the established name. We recommend that the following representation be used for this product:

      Seroquel (quetiapine) extended-release tablets, xx mg*

      *present as xx mg of quetiapine fumarate.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager for Quality, at (301) 796-2055.

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

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/s/

Ramesh Sood

12/13/2006 04:19:39 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-047

AstraZeneca Pharmaceuticals LP
Attention: Gerald L. Limp
Manager, Marketed Products Group
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850

Dear Mr. Limp:

Please refer to your New Drug Application (NDA) dated and received July 17, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) sustained-release 50 mg, 200 mg, 300 mg, and 400 mg tablets.

The Division of Medication Errors and Technical Support (DMETS) and the Division of Psychiatry Products have the following comments and recommendations in regard to your proposed tradename of Seroquel SR:

DMETS is concerned with the potential for confusion between the proposed extended-release tablet called Seroquel SR and the existing immediate-release tablet of quetiapine called Seroquel. Additionally, DMETS does not recommend use of the modifier 'SR' for this product.

1. Extension of an Existing Product Line

   Post-marketing experience has shown that the introduction of product line extensions result in medication errors especially when there is an overlap in strengths, dosing interval, and a knowledge deficit with respect to the introduction of the new extended-release formulation. Moreover, it is common for modifiers to be omitted[1]. In this case, if the SR modifier is omitted it is almost certain that Seroquel will be dispensed because of the overlapping product characteristics. Seroquel SR and Seroquel overlap in established name (Quetiapine), indication (schizophrenia), product strength (50 mg, 200 mg, 300 mg, and 400 mg), route of administration (oral), and dosage form (tablet).

[1] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

In addition, both Seroquel SR and Seroquel share an overlapping target dose. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. However, the two drugs differ in dosing frequency (once daily vs. two to three times daily). DMETS is concerned with the potential consequences of a medication error if a prescription for Seroquel is filled with Seroquel SR or vice versa because the modifier may not adequately minimize confusion between these products. However, according to the sponsor, even if the two dosage forms (Seroquel given twice daily and Seroquel SR given once daily at the same daily dose) are inadvertently switched for one another, the total daily dose is comparable over a 24-hour time period and is unlikely to result in any untoward effects. DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation and understand the differences between the immediate-release and extended-release Quetiapine products. Moreover, all product labeling should include a descriptor indicating how the product should be dosed (e.g., "Once-A-Day Dosing" and "Twice-A-Day Dosing") for the existing products to minimize the potential for confusion. Even with this labeling, we will likely see errors. Therefore, the ideal approach to minimizing this type of confusion would be to request the sponsor reformulate so that the product strengths do not overlap.

2. "SR" Modifier

With respect to the use of the modifier SR, DMETS is concerned that the modifier may be ambiguous and not convey the dosing or formulation differences between the immediate-release (two to three times a day) and extended-release (once daily) products.

We recognize that the accepted practice to convey differences in product formulations is to include an appropriate modifier. We also acknowledge there are nine prescription products listed in the Orange Book which use the "SR" modifier (Wellbutrin SR, Indocin SR, Dilatrate-SR, Ritalin-SR, Oramorph SR, Cardene SR, Pronestyl SR, Rythmol SR, and Isoptin SR. Three of these products (Indocin SR, Dilatrate SR, and Isoptin SR) can be dosed once a day, while the other products are dosed either two or more times a day. Since the currently marketed products have a wide range of dosing intervals, this suffix is ambiguous and does not convey to healthcare practitioners that the product should be dosed on a daily basis. Furthermore, this confusion can be compounded because Seroquel and Seroquel SR have overlapping product strengths (50 mg, 200 mg, 300 mg, and 400 mg), dosage forms (tablet) and target doses. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. There is post-marketing evidence of modifier confusion between Wellbutrin/Wellbutrin SR, Cardene/Cardene SR, and Ritalin/Ritalin SR which all have similar overlapping product profiles as Seroquel and Seroquel SR and utilize the SR modifier.

Moreover, the July 20, 2006, IOM Report "Preventing Medication Errors" recommendation number four, urges FDA to standardize abbreviations, acronyms, and terms to the extent possible. Because the modifier SR can have several meanings it may be beneficial to use a modifier that has been reserved for only once a day dosing.

DMETS does not recommend the use of the proposed suffix "SR" to represent this once-a-day product. A modifier that has been used only for once daily dosing should be employed. Furthermore, because modifiers can be omitted from prescriptions, we request that the product labels and labeling include a descriptor indicating how the product should be dosed (e.g., "Once-A-Day Dosing" and "Twice-A-Day Dosing") for the existing products to minimize the potential for confusion.

Therefore, we request that you submit another proposed proprietary name for evaluation.

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
11/1/2006 01:48:43 PM

Updegraff, Kimberly

From: Updegraff, Kimberly
Sent: Friday, September 15, 2006 2:43 PM
To: 'norbert.ealer@astrazeneca.com'
Subject: Seroquel SR (22-047)

Attachments: filing letter.doc

filing letter.doc (32 KB)

Hello. I am a new project manager working with Division of Psychiatry Products at the FDA. I am assigned the NDA 22-047 for Seroquel SR. The initial review team has requested a few pieces of information to aid in the review process. The requested information can be found in the attachment. Please let me know if you need any additional information or have any questions.

Thank you.

Kimberly Updegraff,B.S.,R.Ph.,M.S.
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation
Phone: (301)796-2201
Fax: (301)796-98378
Email: Kimberly.Updegraff@fda.hhs.gov

Please provide the following:

1. Results of a worldwide literature search, including methodology and warrant that no relevant papers or issues that would adversely affect the conclusions about the safety profile were found, if this was the case
2. Death and Serious Adverse Event (SAE) line listings and associated narratives for all Phase I and II studies (e.g., Studies 036, 037, 086, 118, 001, 003, 097, 008, 087, 098, 109, 145, 115, and 116)
3. Enumeration of dropouts due to adverse events by adverse event and treatment for all Phase I and II studies (e.g., Studies 036, 037, 086, 118, 001, 003, 097, 008, 087, 098, 109, 145, 115, and 116)
4. Adverse event thesaurus (e.g., listing of preferred terms with their associated verbatim terms)
5. Enumeration of common adverse events (>2% Table) for the Safety Population. This should follow the format of Table S-17 on pages 475-476 of 1238 the Summary of Clinical Safety, but include all adverse events that had an incidence of >2%.
6. For the Safety Population, enumeration of other pre-marketing adverse events not reported in the >2% Table described in #5 above. This should follow the format of Table S-17 on pages 475-476 of 1238 the Summary of Clinical Safety.
7. Line listing of all dropouts due to laboratory value abnormalities
8. Line listing of all dropouts due to vital sign abnormalities
9. Line listing of all dropouts due to ECG abnormalities

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/s/

Kimberly Updegraff
9/27/2006 02:09:48 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-047

AstraZeneca Pharmaceuticals LP
Attention: Gerald Limp
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19850-8355

Dear Mr. Limp:

Please refer to your July 17, 2006 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel SR (quetiapine fumarate) 50mg, 200mg, 300mg, and 400mg sustained-release tablets.

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

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at (301) 796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
9/7/2006 09:02:14 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-047

NDA ACKNOWLEDGMENT

AstraZeneca Pharmaceuticals LP
Attention: Greg P. Horowitz, PhD
Executive Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Horowitz:

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

Name of Drug Product:	Seroquel® (quetiapine fumarate) 50 mg, 200 mg, 300 mg and 400 mg Sustained-Release Tablets
Review Priority Classification:	Standard (S)
Date of Application:	July 17, 2006
Date of Receipt:	July 17, 2006
Our Reference Number:	NDA 22-047

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 September 15, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 17, 2007.

Please cite the NDA number listed above 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 Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call LT Felecia Curtis, RN, Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

LT Felecia Curtis, RN,
Regulatory Product Manager
Division of Psychiatry Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

Felicia Curtis

7/25/2006 08:04:08 AM

AstraZeneca

Date: JUN 2 1 2006

US Food and Drug Administration (360909)
Mellon Client Service Center
Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

RE: NDA 22-047
SEROQUEL® SR (quetiapine fumarate sustained-release) Tablets
Prescription Drug User Fee Payment: User Fee I.D. No. PD3006596

Dear Madam/Sir:

In accordance with section 736 of the Federal Food, Drug and Cosmetic Act, AstraZeneca Pharmaceuticals LP (AstraZeneca) is providing a Prescription User Fee payment for a New Drug Application (NDA) for the use of SEROQUEL® SR (quetiapine fumarate sustained-release) Tablets.

The User Fee payment is made in the amount of $767,400 and represents the total NDA application fee for fiscal year 2006. A copy of the User Fee Cover Sheet, Form FDA 3397, is enclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Pat Patterson, Regulatory Affairs Manager, at (302) 885-1539.

Sincerely,

Patricia Patterson for

Gerald Limp,
Regulatory Affairs Director
Regulatory Affairs
Telephone: (302) 886-8017
Fax: (302) 886-2822

JAB

Enclosure

Form FDA 3397 – User Fee Cover Sheet
User Fee Check No. 1500109129

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

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

1. APPLICANT'S NAME AND ADDRESS

ASTRAZENECA PHARMACEUTICALS LP
Gerald Limp
1800 Concord Pike P. O. Box 8355
Wilmington DE 19803-8355
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22047

2. TELEPHONE NUMBER
302-886-8017

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

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:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
SEROQUEL SR Tablets (quetiapine fumarate sustained-release)

6. USER FEE I.D. NUMBER
PD3006596

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, 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
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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Patricia Fitterman for Gerald Limp	Regulatory Affairs Director	JUN 2 1 2006

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

TABLE OF CONTENTS **PAGE**

1. FDA/SPONSOR DISCUSSIONS

Date	Discussions
August 27, 1999	AstraZeneca submitted a proposal to FDA for the development of a sustained-release (SR) formulation of quetiapine, available as 200 mg, and 300 mg tablets. The planned NDA would be supported by pharmacokinetic data (without additional clinical efficacy trials) to demonstrate the bioequivalence of the quetiapine SR tablets with the approved immediate-release (IR) tablets. Clinical efficacy would be extrapolated from the efficacy data for quetiapine IR tablets.
October 21, 1999	FDA concluded that a development program based solely on pharmacokinetic data was insufficient because the SR formulation of quetiapine (given once daily) would not have the same C_{max} or T_{max} as the comparable dose of the IR formulation (given 2 or 3 times daily). Therefore, FDA would require one positive placebo-controlled clinical study to demonstrate effectiveness.
January 30, 2001	AstraZeneca submitted a protocol for a pivotal efficacy study 5077IL/0041, entitled "A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Sustained-release Formulation Quetiapine Fumarate (SEROQUEL) and Placebo in the Treatment of Patients with Schizophrenia." The primary objective of this study was to compare the efficacy of quetiapine SR to placebo in the treatment of patients with schizophrenia.
August 28, 2001	AstraZeneca proposed that preclinical studies of the SR formulation are unnecessary because the excipients in the SR tablets are NF or USP grade components commonly utilized in pharmaceutical products and because the SR and IR tablets are bioequivalent with respect to AUC(0-24h), with the Cmax of the SR tablets being substantially lower than that of the IR tablets. AstraZeneca also requested deferral of pediatric studies in the SR formulation until additional data have been collected on the safety and efficacy of the approved IR tablets in pediatric patients.
March 29, 2002	AstraZeneca submitted a request for a pre-NDA meeting with FDA to discuss the content and format of the NDA. This submission also provided a briefing document and introduced the development of the 50 mg and 400 mg strength tablets.
May 10, 2002	FDA offered AstraZeneca a pre-NDA meeting date of June 20, 2002.

Date	Discussions
June 11, 2002	AstraZeneca submitted additional information in preparation for the June 20, 2002 pre-NDA meeting. Because some of the questions submitted in the March 29, 2002 briefing document were essentially identical to questions the FDA addressed at an April 18, 2002 meeting for the SEROQUEL Bipolar Mania sNDA, AstraZeneca proposed to limit the questions for discussion on June 20, 2002 to those that were not addressed at the Bipolar Mania meeting.
June 20, 2002	A pre-NDA meeting was held between FDA and AstraZeneca to discuss the content and format of the quetiapine SR schizophrenia NDA. Results from the meeting included the following: • FDA agreed that the responses provided at the April 18, 2002 pre-sNDA meeting for Bipolar Mania would apply to the similar questions submitted in the pre-NDA briefing document for quetiapine SR. • FDA agreed to deferral of pediatric studies of quetiapine SR, and commented that a controlled clinical study of quetiapine SR in pediatric patients may not be necessary. • FDA agreed that no preclinical animal data were required, provided the to-be-marketed formulations of quetiapine SR have AUCs that are similar to the current marketed IR formulations. • FDA commented that the submission should include a comparison of quetiapine SR and IR safety data for the titration period, ie, for each treatment arm, comparing vital sign measurements and adverse events over the first week. • FDA agreed that pooling of data from the clinical pharmacology and biopharmaceutic trials of queitiapine SR with data from Study 041 was not necessary. • FDA agreed that postmarketing safety data does not need to be included in the NDA because postmarketing safety data on the IR formulation is relevant to the SR formulation and the FDA already has access to this data through PSURs. • FDA requested a comprehensive analysis of any effects on glucose levels observed with quetiapine. • FDA indicated that the deadline for submission of the 4-month safety update could be extended up to 6 months, if it meant complete unblinded datasests could be provided for the ongoing studies.

Date	Discussions
December 12, 2002	AstraZeneca officially notified FDA of its decision to place the filing of the planned NDA on hold for business purposes and that the analysis of Study 5077IL/0041 was ongoing.
June 7, 2004	AstraZeneca requested FDA feedback on an expanded clinical development program to support the worldwide registration of quetiapine SR for the treatment of schizophrenia. This program included two efficacy studies of similar design (D144C00133 to be conducted in the US and D144C00132 to be conducted outside of the US), a safety/tolerability study to address the dose escalation schedule utilized in the subsequent studies (D1444C00145), and an IR-to-SR switching study (D1444C00146). It also included a comparator-to-SR switching study (D1444C00147) and a Phase 4 commitment study to NDA 20-639 (D1444C00004); the results of these studies would be reported in the 4-month safety update. The protocol for D1444C00133 was officially submitted to the IND.
November 2, 2004	AstraZeneca submitted a new protocol for Study D1444C00148, entitled "A 6-week, Double-blind, Randomized, Parallel-group, International, Multi-center, Phase III Study Comparing the Efficacy and Safety of Sustained-Release and Immediate-Release Quetiapine Fumarate (SEROQUEL) to Placebo in the Treatment of Agitation Associated with Alzheimer's Dementia in Elderly Residents of Long-term Care Facilities.
January 14, 2005	During a pre-sNDA meeting between FDA and AstraZeneca to discuss the SEROQUEL Bipolar Depression program, AstraZeneca had the opportunity to request FDA input on the SR schizophrenia program. Results from the meeting included the following: • FDA confirmed that one positive study (either Study 132 or 133) would be sufficient for NDA approval, even in light of study 5077IL/0041 not meeting its primary endpoints. • FDA agreed that, in light of the recent Pediatric Research Equity Act of 2003, AstraZeneca's previous deferral of pediatric studies with quetiapine SR is still applicable to the revised SR clinical development program.

Date	Discussions
January 26, 2005	FDA provided the following feedback on Study D1444C00148: • The primary variable CGI-S is used to assess global clinical changes, and is not adequately specific for assessing agitation. The primary efficacy variable should include a specific agitation scale as well as the CGI if the sponsor wishes to use this study to support efficacy. • If the goal is to show efficacy for monotherapy, then the study is not adequately designed for this objective, given that concomitant psychotropic agents are allowed. Subsequently, AstraZeneca placed the study on hold to further evaluate its design.
May 13, 2005	During an End of Phase II meeting between FDA and AstraZeneca to discuss the proposed clinical development for the Major Depressive Disorder/Generalized Anxiety Disorder program, FDA confirmed that the Columbia University approach to analysis of suicidality would be required for the quetiapine SR schizophrenia program. FDA commented that it was not necessary for this analysis to be conducted by experts at Columbia University; this could be conducted in-house or by another contractor.
August 8, 2005	AstraZeneca requested a pre-NDA meeting with FDA to discuss content and format of the planned NDA for quetiapine SR in schizophrenia.
August 18, 2005	FDA granted a pre-NDA meeting for October 13, 2005.
September 12, 2005	AstraZeneca submitted the pre-NDA briefing document that provided information related to the clinical development program for quetiapine SR in schizophrenia and the planned NDA.
September 15, 2005	AstraZeneca provided the FDA with a briefing document in preparation for an October 26, 2005 CMC pre-NDA meeting.

Date	Discussions
October 11, 2005	FDA provided complete responses to the questions raised in AstraZeneca's pre-NDA briefing document and subsequently canceled the October 13, 2005 meeting. The following key agreements were reached: • Assuming positive results in either Study 132 or Study 133, the study design supports inclusion of the proposed language in the US label. • Complete efficacy data from Study 041 will be provided in the CSR and will be discussed in the Clinical Overview; the results of this study will not be presented in the Summary of Clinical Efficacy due to important design differences compared with Studies 132 and 133. • While FDA does not accept the non-inferiority approach used in Study 146 for demonstrating efficacy, it would not object to some language suggesting that switching to the same total daily dose of an SR formulation was adequately tolerated. • Data presentations in the Summary of Clinical Safety will be based upon 3 pools (placebo-controlled, phase III and dose-escalation) of safety data from Studies 041, 132, 133 and 146. Safety data from a Phase III study in elderly patients with Alzheimer's disease (Study 5077IL/0115) will be summarized briefly in the CTD with full details available in the CSR. Safety data from pharmacokinetic and clinical pharmacology studies will be summarized separately from the data from the efficacy studies. • Patient narratives and lists of investigators will be included in the individual CSRs and will also be aggregated into higher-level documents within the CTD. • The requirements of Section 2.7.4.6 of the CTD regarding postmarketing data are not applicable to quetiapine SR. • Available safety data information from Studies 147 and 004 will be provided in the 4-month safety update • (b) (4) • Information in the CTD that pertain to nonclinical pharmacology and toxicology will be cross-referenced to information contained within NDA 20-639. FDA offered to resolve any clarifications via e-mail.

Date	Discussions
October 26, 2005	A CMC pre-NDA meeting was held between FDA and AstraZeneca to discuss issues related to the quetiapine SR schizophrenia NDA: • FDA asked if AstraZeneca considered submitting Seroquel SR as part of their pilot program. • FDA stated that a decision on whether AstraZeneca has achieved a level A IVIVC is a review decision. However no concerns were identified with the information presented. In fact, it was suggested that the data looked very good. FDA provided AstraZeneca with suggestions on information they would expect to see in the NDA. • The concept of the formulation design was accepted. However, the limits of AstraZeneca's operating space will be a review issue. The FDA provided AstraZeneca with numerous suggestions on data they would like to see in the submission. • There were no concerns with AstraZeneca submitting as little as 3 months accelerated and long term stability data for Macclesfield. However, AstraZeneca must bridge the Macclesfield data to existing data from Newark. In particular, a comparison to non-debossed tablets is critical. • FDA recommended that AstraZeneca not include a comparability protocol for additional drug product manufacturing sites in the NDA.
October 31, 2005	AstraZeneca submitted statistical analysis plan (SAP) for Study D1444C00133.
November 4, 2005	AstraZeneca requested FDA to provide clarification on some of its responses to the original pre-NDA questions.
November 9, 2005	AstraZeneca submitted the SAP for the Common Technical Document (CTD) for the registration of quetiapine SR in schizophrenia.
December 19, 2005	AstraZenea submitted a request to FDA for evaluation of the SEROQUEL SR proprietary name.
January 30, 2006	AstraZeneca submitted SAP for Study D1444C00132.
February 7, 2006	Via telephone contact, AstraZeneca agreed to provide an outline and short description of the intended P.2 section for the NDA. FDA agreed to review and comment on the document.

Date	Discussions
March 15, 2006	AstraZeneca submitted the P.2 document to FDA.
March 20, 2006	FDA provided feedback on SAP for Study D1444C00132.
March 31, 2006	AstraZeneca submitted response to FDA's feedback on SAP for Study D1444C00132.
April 5, 2006	AstraZeneca requested FDA's agreement on specific programming issues related to Case Report Tabulations (CRTs) in the NDA submission.
April 6, 2006	Via telephone contact, FDA responded to the P.2 document submission of March 15, 2006
April 20, 2006	FDA provided clarification to its responses to AstraZeneca's pre-NDA questions, including: • Results from the PK study 0097 and one pivotal efficacy study are sufficient for filing or a claim regarding switching from IR to SR, however, the labeling language would not agreed prior to review of the NDA. • Only routine risk-management may be needed to satisfy FDA's requirements regarding risk management activities (including routine risk management and RiskMAPs) for the quetiapine SR program, though it is a matter of review.
April 20, 2006	FDA agreed that submission of the final clinical study report for Study D1444C0004 as a supplement to NDA 20-639 will not impact the PDUFA review cycle for the quetiapine SR NDA.
May 31, 2006	FDA agreed with AstraZeneca's proposals (as described in the April 5, 2006 e-mail correspondence) for providing CRTs in the NDA submission and referred AstraZeneca to the Guidance for Industry regarding eCTD specifications for placement of these data.