DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

March 27, 2012

Kevin McKenna, Ph.D.
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Washington, DC 20004-2401

Dear Dr. McKenna:

AstraZeneca submitted a citizen petition asking that the Food and Drug Administration (FDA) "not approve any quetiapine abbreviated new drug application (ANDA) for which Seroquel is the reference listed drug (RLD)" if the proposed labeling for the ANDA omits information that FDA required AstraZeneca to include in the labeling for Seroquel.[1] Because the Petition was submitted in accordance with 21 U.S.C 355(q), FDA was required to respond within 180 days. See 21 U.S.C. 355(q)(1)(F). On March 7, 2012, FDA denied the Petition without comment on its merits because it had not yet made a final determination on the issues raised by the Petition and was not required to do so before it was ready to act on a pending ANDA.[2]

Rather than filing a petition for reconsideration, AstraZeneca sued FDA on March 12, 2012, alleging that FDA violated the Administrative Procedure Act by acting arbitrarily, capriciously, and not in accordance with law, and abusing its discretion in denying AstraZeneca's Petition.[3] On Friday, March 23, the Court denied AstraZeneca's Application for Preliminary Injunction and dismissed the action without prejudice, stating that, "the Court has no doubt that the substantive issues raised by AstraZeneca in this action are not presently fit for judicial review."[4]

Today, FDA approved ANDAs for generic versions of Seroquel. Now that FDA has considered AstraZeneca's allegations in the context of specific ANDA approvals for Seroquel, and in light of representations the agency has made to the court that it will provide Astra Zeneca notice of its decision,[5] we are writing as a courtesy to inform you of our conclusions in this matter. This

[1] Letter from Kevin McKenna, Ph.D., Vice President, Regulatory Affairs, AstraZeneca to Division of Dockets Management, Food and Drug Administration dated September 2, 2011 (Petition) (Docket No. FDA 2011-P-0662).

[2] Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research to Kevin McKenna, Ph.D., Vice President, Regulatory Affairs, AstraZeneca dated March 7, 2012, at 4-5. (FDA Petition Response) (Docket No. FDA 2011-P-0662).

[3] *See* Compl. for Declaratory & Injunctive Relief, ECF No. [1], 98. On the same day it commenced the action, AstraZeneca filed an Application for Preliminary Injunction asking the Court to enjoin FDA from giving final approval to a generic version of Seroquel or Seroquel XR.

[4] *AstraZeneca Pharms. LP v. FDA*, No. 12-cv-00388 (D.D.C.) (Mem. Op. at 19) (Dkt. # 15-16). The court later denied AstraZeneca's motion to amend its decision to order FDA to provide AstraZeneca with advance notice of any ANDA approval. (Order dated Mar. 26, 2012) (Dkt. # 20).

[5] FDA Surreply at 2 n.1.

letter has been prepared in consultation with the Office of New Drugs (OND) and the Office of Generic Drugs (OGD).

AstraZeneca identified three portions of labeling that it argued are essential to the safe use of quetiapine for any purpose: (1) Table 2, which consists of metabolic effects data; (2) the boxed warning on suicidality; and (3) Section 5.2 warnings on clinical worsening and suicide risk. (For ease of reference, the boxed warning and Section 5.2 warnings are referred to collectively throughout as "suicidality warnings.") AstraZeneca has also asserted that Table 2 is protected by 3-year exclusivity such that approval of an ANDA referencing Seroquel may not occur until on or after December 2, 2012, when the last exclusivity period on a ***different*** AstraZeneca product -- Seroquel XR -- expires.[6]

FDA concurs that these portions of the labeling are essential to safe use of a generic quetiapine product referencing Seroquel for any indication, and the agency would not approve a quetiapine ANDA referencing Seroquel that omitted them. FDA does not concur, however, that an ANDA referencing Seroquel is precluded from including Table 2 or the suicidality warnings by virtue of AstraZeneca's 3-year exclusivity on certain indications for Seroquel XR.

I. FACTUAL BACKGROUND

On September 26, 1997, FDA approved AstraZeneca's new drug application (NDA) for Seroquel (quetiapine fumarate) Tablets (Seroquel) (NDA 020639) for the treatment of manifestations of psychotic disorders. On March 27, 2001, FDA approved a supplement to the NDA changing the labeling to more clearly state that the drug is indicated for the treatment of schizophrenia.

FDA approved the addition of the following bipolar adult patient populations to the labeling on the following dates:

- January 12, 2004 - Monotherapy in the treatment of acute manic episodes associated with Bipolar I disorder, and Adjunctive therapy with mood stabilizers (lithium or divalproex) in the treatment of acute manic episodes associated with Bipolar I disorders (S-016, S-017)
- October 20, 2006 - Monotherapy for the acute treatment of depressive episodes associated with bipolar I disorder (S-026)
- May 13, 2008 - Maintenance treatment of bipolar I disorder, as an adjunct to lithium or divalproex (S-037)

AstraZeneca received 3-year exclusivity for each of these new patient populations, which has now expired.

Because quetiapine has antidepressant effects, the class warnings regarding suicidality were added to Seroquel on October 20, 2006, in conjunction with its approval as monotherapy for the acute treatment of depressive episodes associated with bipolar I disorder. These warnings were

[6] Although it is unclear whether AstraZeneca asserts that the suicidality warnings are also protected by AstraZeneca's 3-year exclusivity for Seroquel XR, we address that possibility in this letter as well.

based on FDA's meta-analyses of antidepressant data for multiple second generation antidepressants.[7]

On December 2, 2009, FDA approved two new pediatric indications for Seroquel (S-045, S-046):

- Adolescents (ages 13 to 17) for the treatment of schizophrenia; and
- Adolescents and children (ages 10 to 17) for the acute treatment of manic episodes associated with bipolar I disorder, both as a monotherapy and as an adjunct to lithium or divalproex.

AstraZeneca received new patient population exclusivity and 6 months of pediatric exclusivity for these two pediatric indications (or new pediatric patient populations), which expire on June 2, 2013.

FDA requested glucose-related metabolic data for Seroquel by letter dated January 8, 2008. AstraZeneca provided these data, which are now presented in "Table 2: Fasting Glucose – Proportion of Patients Shifting to >126 mg/dL in short-term (≤ 12 Weeks) Placebo-Controlled Studies," on June 26, 2008. AstraZeneca submitted these data in a letter coded by FDA as general correspondence, not as a prior approval supplement (PAS) or a Changes Being Effected ("CBE") supplement to the Seroquel NDA.[8] In the course of approving the prior approval supplements (S-045, S-046) for the pediatric indications noted above on December 2, 2009, FDA incorporated Table 2 into the revised labeling it approved on that date.[9]

Table 2 is a composite table of safety data derived from 15 clinical trials conducted in adults in multiple psychiatric populations. Of the 15 trials, 9 were conducted using Seroquel XR exclusively. None were conducted in pediatric populations, including those pediatric populations for which exclusivity was granted at the time Table 2 was added to the Seroquel labeling. The majority were conducted in healthy volunteers or patient populations for which Seroquel is not approved. No exclusivity was granted to Seroquel in association with the addition of this table to the Seroquel labeling.

The FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) lists one patent for Seroquel: U.S. Patent No. 4,879,288 (the '288 patent). The '288 patent is listed as containing drug substance, drug product, and use claims, and its use code is for the

[7] The issue of how broadly to apply warning language was discussed at the September 2004 joint meeting of the Psychopharmacologic Drugs and Pediatric Advisory Committees, and there was a clear consensus that the risk statements should apply to all drugs that could be considered "antidepressants" whether or not there were data directly implicating a particular drug, and regardless of the indication(s) for which a drug was approved. *See generally* Transcript of the Joint Meeting of the Psychopharmacologic Drugs and Pediatric Advisory Committees (Sept. 14, 2004) at 264-333.

[8] FDA regulations on prior approval supplements and CBE supplements are set forth in 21 CFR 314.70.

[9] The two approval letters for the two new pediatric indications (S-45, S46) reflect that FDA consolidated a number of other actions at the same time as well. The letters provide that "[w]e also note that your "Changes Being Effected" supplemental applications submitted on July 11, 2008, September 11, 2008, December 4, 2008 and your "Prior Approval" supplement submitted on July 19, 2007 have been superseded by this approval action." (redactions omitted).

treatment of bipolar disorder and schizophrenia. The '288 patent is listed as expiring on September 26, 2011, with a 6-month pediatric exclusivity period expiring on March 26, 2012.[10]

On or after March 26, 2012, the two pediatric population exclusivities (and corresponding pediatric exclusivity) will be the only exclusivities listed in the Orange Book for Seroquel.

Information about the current patent and exclusivity protection for Seroquel is summarized below.

Approved Indications	**Approval Date**	**Patent/ Exclusivity**	**Expiration Date**
Schizophrenia in adults	9/26/97 3/17/01 (clarified)		
Bipolar I mania - acute treatment as mono and adjunct (S-16, S-17)	1/12/04	*expired*	
Bipolar I depression - acute treatment (as mono) (S-26)	10/20/06		
Bipolar I - maintenance treatment as adjunct (S-37)	5/13/08		
Bipolar and schizophrenia		'288 patent	*expired*
PEDS Schizophrenia 13-17	12/2/09	NPP	6/2/13
PEDS Bipolar mania 10-17			

Since Seroquel's approval in 1997, AstraZeneca has enjoyed approximately 15 years of multiple exclusivity and patent protections resulting in no generic competition.

II. LEGAL/REGULATORY BACKGROUND

A. ANDA Approval

The 1984 Hatch-Waxman Amendments created section 505(j) (21 U.S.C. 355(j)) of the Federal Food, Drug, and Cosmetic Act (the Act), which established the ANDA approval process. To obtain approval, an ANDA applicant is not required to submit independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's

[10] The '288 patent was challenged and found by the United States District Court for the District of New Jersey, as affirmed by the Federal Circuit, to be valid and infringed as to all of the ANDA filers. *AstraZeneca Pharms. LP v. Teva Pharms. USA, Inc.*, 567 F. Supp. 2d 683 (D.N.J. 2008); aff'd 583 F.3d 766 (Fed. Cir. 2009).

previous finding that the reference listed drug (RLD or innovator) is safe and effective.[11] Under section 505(j) of the Act, an ANDA must include information to show that, among other things, the proposed product is bioequivalent to the RLD and has the same active ingredient, dosage form, strength, route of administration, and, with certain permissible differences, labeling as the RLD (21 U.S.C. 355(j)(2)(A)(v)). The agency must approve an ANDA unless it finds, among other things, the ANDA does not include sufficient evidence of the foregoing (21 U.S.C. 355(j)(4)).

The Act requires an ANDA to contain "information to show that the labeling proposed for the new (generic) drug is the same as the labeling approved for the [reference] listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (21 U.S.C. 355(j)(2)(A)(v)). A parallel provision appears in section 505(j(4)(G) of the Act.

FDA's implementing ANDA labeling regulations (at 21 CFR § 314.94(a)(8)(iv)) provide:

> Labeling . . . proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 312.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These differences include the following:

> …differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, *or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity* under section 505(j)(4)(D) of the act [now section 505(j)(5)(F)].

Section 314.127(a)(7) of FDA regulations further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are protected . . . by exclusivity," FDA must find that the "differences do not render the proposed [generic] drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."

FDA often refers to patent- and exclusivity-related changes in the labeling of a generic product as "carveouts." Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement.[12]

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[11] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's Orange Book.

[12] *See e.g.*, *Bristol Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F .3d 141, 148, fn. 3 (4th Cir. 2002).

B. Three-Year Exclusivity

1. Summary of Statutory and Regulatory Framework for 3-Year Exclusivity

FDA regulations (at 21 CFR §§ 314.50(j) and 314.70(g)) require NDA applicants to submit for original NDAs and NDA supplements a statement regarding any claimed exclusivity, including 3-year exclusivity. Exclusivities, including 3-year exclusivity, are published in the Orange Book to put ANDA and 505(b)(2) applicants on notice regarding the scope and expiration dates of potential barriers to approval. FDA implementing regulations (at 21 CFR 314.94(a)(3)(i)) require ANDA applicants to submit a "statement as to whether, according to the information published in the list, the [RLD]" is entitled to a period of marketing exclusivity.

Section 505(j)(5)(F)(iv) of the Act establishes 3-year exclusivity (vis-à-vis ANDAs) for certain changes to new drugs made through supplements to NDAs when such changes are based on new clinical investigations, other than bioavailability studies, that are essential to the approval of the change. It states:

> If a supplement to an application approved under subsection (b) is approved after the date of enactment of this subsection [enacted September 24, 1984] and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an [ANDA] for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

The statute does not define what types of new clinical investigations are essential to the approval of the supplement. FDA regulations define "new clinical investigation" as:

> [A]n investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

21 C.F.R. § 314.108(a).

The preambles to the proposed and final regulation make clear that not every piece of labeling information that was based on a clinical investigation or included in a supplement will be entitled to 3-year exclusivity protection. For example, the preamble to the 1989 proposed rule, in recognition of Congressional intent, states:

> Congress understood that the substantial economic rewards of exclusivity might well encourage drug companies to make minor and unimportant alterations in their marketed drug products or to conduct additional tests which they could claim provide important new information about a marketed drug product. To avoid rewarding such behavior, the 3-year provision includes

> the special criteria intended to restrict eligibility to significant innovations. See Cong. Rec. H9114, 9124 (daily edition September 6, 1984) (statement of Representative Waxman); Cong. Rec. S10505 (daily edition August 10, 1984) (statement of Senator Hatch).

54 Fed. Reg. 28872, at 28896 (July 10, 1989).

FDA noted that the types of changes that are likely to merit 3-year exclusivity "are the types of changes in a drug product that require prior approval by FDA before the change may be made." *Id.* at 28899.

Furthermore, the preamble to the proposed rule states that, "[s]tudies that establish new risks will not be eligible for exclusivity because protection of the public health demands that all products' labeling contain all relevant warnings." *Id.* The preamble to the final rule similarly affirmed:

> Changes that would not warrant exclusivity are, as discussed in the preamble to the proposed rule, changes in labeling that involve warnings or other similar risk information that must be included in the labeling of generic competitors. Applicants obtaining approval for such changes in labeling would, in any event, have no valid interest in precluding such information from the labeling of other products. Furthermore, FDA does not consider a study to be "essential to approval" simply because the applicant conducted it and submitted the study for agency review.

59 Fed. Reg. 50338, at 50357 (Oct. 3, 1994).[13]

Three-year exclusivity is sometimes referred to as "new patient population" exclusivity because it is often associated with a new indication or a new population (such as a new age group). Three-year exclusivity may also be granted for changes such as new combinations of older products, new esters, new strengths, and new dosage forms.

The statute sets up a relationship between the "new clinical investigations" that are "essential to the approval of the supplement," and the scope of exclusivity. That is, if an applicant submits a supplement and gets 3-year exclusivity for a change in the use of the drug product supported by new clinical investigations, the FDA may not approve an ANDA referencing that drug product for the "change approved in the supplement" during that 3-year exclusivity period. Because the change in the drug product or use of the drug product that was approved in the supplement was based at least in part on the new clinical investigations, it naturally follows that the scope of any exclusivity also will relate to the scope of those new clinical investigations.

[13] FDA also quoted Representative Henry Waxman's statement that three-year exclusivity was intended to "encourage drugmakers to obtain FDA approval for significant therapeutic uses of previously approved drugs" (130 Congressional Record H9114, (Sept. 6, 1984)). 59 Fed. Reg. at 50357. FDA stated that "an applicant is not entitled to 3-year exclusivity merely because it supplements an approved application based in part on a clinical investigation or because it certifies to FDA that the clinical investigation is essential to approval of the application or supplement." *Id.*

FDA's regulation similarly emphasizes a relationship between the change in the use of the drug product supported by the supplement and the scope of the exclusivity that the supplement earns. The regulation provides that the agency will not approve an ANDA referencing a drug product for three years if the ANDA "relies on [] information supporting a change approved in the supplemental new drug application." 21 C.F.R. § 314.108(b)(ii)(5). The regulation, in context with the definition for "new clinical investigation," emphasizes this relationship between the information from the new clinical investigation, the change approved in the supplement, and the scope of what the ANDA seeks to rely on for approval.

2. Summary of Agency Approach to 3-Year Exclusivity

In interpreting the statute and the regulations, FDA has long determined the scope of 3-year exclusivity on a case-by-case and product-by-product basis, depending on the particulars of the relationships between the information from the "new clinical investigation," the change approved to the drug product, and the scope of what an ANDA relies on.[14] For example, FDA has permitted an ANDA or 505(b)(2) applicant referencing a product with 3-year exclusivity for a new indication to include relevant safety labeling information from trials that were conducted to support approval of that indication. Typically, the agency has done so if the information is not unique to that indication and if the labeling does not identify the indication in which the trial from which the safety information was generated was conducted.[15]

Courts who have considered the matter have affirmed FDA's interpretation of the scope of 3-year exclusivity.[16]

III. ANALYSIS

FDA concludes that certain information -- Table 2 and the suicidality warnings -- is essential to the safe use of a generic quetiapine product referencing Seroquel, is not protected by any 3-year exclusivity period, and generic quetiapine products referencing Seroquel will be expected to bear labeling that includes the information.

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[14] *See e.g.,* FDA Letter in Docket No. FDA-2010-P-0164 regarding Colcrys (colchicine) (noting that "the actual scope of [3-year] exclusivity" is limited to "the conditions of approval for which new clinical investigations were essential").

[15] *See e.g.*, Sandoz's 505(b)(2) NDA for topotecan (which includes tables with pooled adverse reaction data from trials in two indications -- ovarian cancer and small cell lung cancer – because they were important to the safe use of the product for any indication, in spite of the fact that Hycamtin, the NDA referenced, still had unexpired 3-year exclusivity for the ovarian cancer indication). *See also* FDA carve-out decisions for Lyrica (pregabalin) (finding that a table of safety data pooled from studies in multiple patient populations including patent protected indications and additional indications for which Lyrica was not approved, was not protected and could be included in generic labeling notwithstanding sponsor's patent protection on certain indication(s)); Xyzal (levocetirizine) (determining that safety information in Section 6 of labeling was not protected and could be included in generic labeling notwithstanding fact that information was derived from studies in allergic rhinitis, an indication for which sponsor had 3-year exclusivity).

[16] *See Zeneca Inc. v. Shalala*, No. 99-307, 1999 U.S. Dist. LEXIS 12327, at *38 (Aug. 11, 1999), *aff'd*, 213 F.3d 161 (4th Cir. 2000) (upholding FDA's grant of three-year exclusivity as relating only to the clinical investigations for a particular preservative, not to preservatives in general).

A. Table 2

AstraZeneca has asserted that Table 2 includes important safety information for quetiapine and may not be omitted from the generic quetiapine product labeling. Petition at 4. AstraZeneca also contends that Table 2 is protected by 3-year exclusivity through the following reasoning:

- Table 2 was included in the labeling of Seroquel pursuant to labeling supplements to the Seroquel NDA that were approved by FDA;
- These labeling supplements were supported by clinical studies conducted by AstraZeneca with Seroquel XR for the treatment of bipolar disorder and MDD, two indications for which Seroquel XR has 3-year exclusivity;
- AstraZeneca's "protected data" is now contained in the labeling for Seroquel; and
- Because the new clinical investigations with Seroquel XR for the treatment of bipolar disorder and MDD were essential to the approval of the labeling supplement for Seroquel, the labeling for Seroquel is entitled to three years of exclusivity.

Petition at 5. According to AstraZeneca's reasoning, no ANDA can be approved for a generic version of Seroquel for any indication until December 2, 2012, the date of which exclusivity for the MDD indication for Seroquel XR expires.[17]

FDA agrees that Table 2 contains important safety information that must be included in the labeling for any generic quetiapine product referencing Seroquel, but does not agree that it is protected by AstraZeneca's MDD and bipolar 3-year exclusivities for ***another*** AstraZeneca product, Seroquel XR. After 15 years of marketing exclusivity and patent protection for Seroquel, the only remaining protection for Seroquel is 3-year exclusivity for two pediatric indications (or pediatric patient populations) -- and AstraZeneca does not argue that Table 2 is protected by those exclusivities. FDA has determined that no 3-year exclusivity period covers Table 2 for Seroquel.

First, as noted in the preambles to the proposed and final rules, changes in labeling that involve the addition of warnings or other similar risk information are generally not entitled to 3-year exclusivity. Accordingly, composite safety data in drug labeling that happens to be derived from trials in both protected and unprotected indications is generally not entitled to exclusivity protection. Table 2 contains generally applicable safety information and does not identify a protected indication, or any indication at all. As AstraZeneca itself notes, Table 2 "is not broken down by indication or formulation and was intended to be considered by physicians prescribing Seroquel for any of its approved uses." Petition at 3. On this basis alone, the inclusion of Table 2 in generic quetiapine product labeling is justified and consistent with applicable law and agency precedent.

[17] This reasoning would also conveniently dictate that, if AstraZeneca received exclusivity for another indication for Seroquel XR in the future and information from studies in that indication were added to Table 2 in the Seroquel labeling, no ANDA referencing Seroquel for any of the non-protected indications would be eligible for approval until that exclusivity also expires.

An analysis of Table 2 further undermines AstraZeneca's claim. Table 2 is reproduced in its entirety below:

Table 2: Fasting Glucose—Proportion of Patients Shifting to ≥ 126 mg/dL in short-term (≤ 12 weeks) Placebo-Controlled Studies

Laboratory Analyte	Category Change (At Least Once) from Baseline	Treatment Arm	N	Patients n (%)
Fasting Glucose	Normal to High (<100 mg/dL to ≥ 126 mg/dL)	Quetiapine	2907	71 (2.4%)
		Placebo	1346	19 (1.4%)
	Borderline to High (≥ 100 mg/dL and <126 mg/dL to ≥ 126 mg/dL)	Quetiapine	572	67 (11.7%)
		Placebo	279	33 (11.8%)

Table 2 was created from pooled data from 15 clinical trials. Of these trials, 10 of the 15 were conducted exclusively with Seroquel XR. Further:

- 4 relate to patient populations for which neither Seroquel nor Seroquel XR is approved (1 in healthy volunteers and 3 in patients with generalized anxiety disorder).
- 2 relate to schizophrenia, for which neither Seroquel nor Seroquel XR has exclusivity or patent protection.
- 5 relate to bipolar depression or mania.
  - Seroquel has no remaining exclusivity or patent protection for these indications.[18]
- 4 were studies of Seroquel XR as monotherapy in patients with MDD.
  - Seroquel is not approved for any MDD patient population.
  - Seroquel XR is approved only as an *adjunct* to antidepressants in the treatment of MDD and *only* has exclusivity for adjunctive treatment of MDD, not for use as monotherapy in this indication. All 4 of these studies were of quetiapine not as adjunctive therapy for treatment of MDD, but as a *monotherapy*, an indication for which neither Seroquel nor Seroquel XR has approval, let alone exclusivity.

See Appendix 2 for an itemized list of the studies contributing to Table 2.

Second, even if generally applicable safety data in Table 2 could be protected, Seroquel XR's 3-year exclusivity for MDD does not protect Table 2 for Seroquel. The data in Table 2 for Seroquel were not derived from the MDD indication for which AstraZeneca has 3-year exclusivity. AstraZeneca has exclusivity for MDD only as *adjunctive therapy* and the data in

[18] Seroquel XR has 3-year exclusivity related to the bipolar depression and mania patient populations that expires on April 8, 2012.

Table 2 have been derived from *monotherapy trials*. Two adjunctive therapy studies (protocols D1448C00006 and D1448C00007) supported Seroquel XR's approval for the MDD adjunct indication. These and only these two trials were identified as "new" and "essential to approval" of the MDD adjunct indication in the Exclusivity Summary. Therefore, 3-year exclusivity for MDD as adjunctive therapy cannot not protect Table 2.

Third, exclusivity for a new indication can only protect a product that is approved for the protected indication. Seroquel is not approved for MDD and protection for the bipolar indications has expired as of March 26, 2012. AstraZeneca's only remaining exclusivity for Seroquel is for the two pediatric indications. The Exclusivity Summary for the pediatric supplements corresponding to these indications identifies three studies that were essential to approval of that supplement (D1441C00112, 1441C00149, and 1441C00150), none of which contributed data to Table 2. In other words, Table 2 includes no information from indications for which Seroquel has protection and does not even include pediatric data.

Fourth, *even if* certain data were derived from protected indications it is not necessarily the case that all information added to the labeling at the same time that FDA approves a change to a product (such as new indication) that earns exclusivity is also protected by that exclusivity. As noted elsewhere, in the course of approving the prior approval supplements (S-045, S-046) for the pediatric indications on December 2, 2009, FDA incorporated Table 2 into the revised labeling it approved on that date. However, this timing was only coincidental, and there is no relationship between the exclusivity for the pediatric indications earned on December 2, 2009, and the data in Table 2. This data does not qualify for any protection solely by virtue of the timing of FDA's approval of the supplement, including Table 2. Rather, the scope of exclusivity must relate to the new clinical investigations that were conducted.

Fifth, Table 2 was added to the Seroquel XR labeling at the time of approval of the MDD indication, not the bipolar indications for which Seroquel XR's 3-year exclusivities expire on April 8, 2012.[19] Seroquel XR's 3-year exclusivity for the bipolar indications -- and MDD indication -- has no bearing on the inclusion of Table 2 in the labeling of an ANDA referencing Seroquel, a different drug product, for the reasons stated above.[20]

For all of these reasons, FDA rejects AstraZeneca's argument that Table 2 in the Seroquel labeling is covered by Seroquel XR's 3-year exclusivity.[21]

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[19] Any argument that AstraZeneca might make regarding these 5 trials will be moot as of that date.

[20] Today's decision relates only to Seroquel. For Seroquel XR, there continue to be multiple overlapping exclusivities, two of which expire on April 8, 2012, as well as patent protections. These protections could have implications for carve-out decisions made by a line-by-line review of product labeling which involves consideration of issues beyond Table 2.

[21] AstraZenca states that the agency pointed to the antipsychotics, Invega and Latuda, as "good examples of the format presentation" for Table 2. Petition at 4. There are other drugs in the same class that include the same type of metabolic information in tabular form ("Table 2-like data"). The agency's conclusion that Table 2 is not protected and its implications for generic quetiapine products is consistent with the agency's treatment of other second-generation antipsychotics for which data regarding metabolic changes, including Table-2 like data, have been made. For Janssen Pharmaceuticals Inc.'s (JP's) Risperdal (risperidone) tablets (NDA 20272), the agency approved a supplement (S-066) adding Table 2-like data to the labeling on September 24, 2011. The agency also approved a supplement (S-043) adding Table 2-like data to the labeling for JP's other product, Risperdal Consta (risperidone)

B. Suicidality and Antidepressant Drugs Warnings

AstraZeneca asserts that FDA should not approve a quetiapine ANDA that omits from its labeling important warnings regarding suicidality. Petition at 6. Specifically, AstraZeneca refers to the boxed warning for increased suicidality risk and warnings regarding clinical worsening and suicide risk ("Warnings and Precautions", Section 5.2).

The boxed warning is copied below (the Section 5.2 information is copied in an addendum):

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in patients under ten years of age [*see Warnings and Precautions* (5.2)].

All drugs with antidepressant properties, like Seroquel, bear warnings regarding suicidality risks. FDA agrees that these warnings are essential to the safe use of quetiapine for any purpose. Accordingly, FDA would expect generic quetiapine product labeling to carry the boxed and Section 5.2 suicidality warnings, regardless of the indication for which it is (or is not) approved.

Although it is not entirely clear whether AstraZeneca is asserting that the boxed and Section 5.2 suicidality warnings are protected by any AstraZeneca's exclusivity, to the extent AstraZeneca argues that they are so protected, we disagree for the following reasons:

- The suicidality warnings here are precisely the type of warnings Congress envisioned would not be eligible for exclusivity, in order to protect the public health.

- The suicidality warnings are based on FDA's comprehensive review of approximately 300 trials involving numerous drugs and more than 77,000 patients with depression and other psychiatric disorders. See Section 5.2 of Seroquel labeling. The warnings are not specific to any particular sponsor, drug, or indication, including AstraZeneca and Seroquel.[22]

Long-Acting Injection (NDA 21346), on the same day. The Orange Book lists no exclusivity at all for Risperdal tablets and no exclusivity corresponding to the date on which the information was added to the Risperdal Consta Long-Acting Injection labeling. On November 29, 2011, the agency approved Prinston Inc.'s ANDA (A077493) (now held by Kali Laboratories') for risperidone tablets with the same substantive information. The Table 2-like data was not entitled to exclusivity in the first instance and did not bar approval of a generic product with the same substantive information.

[22] The suicidality warnings were approved for Seroquel on October 20, 2006 (S-026), as part of the Seroquel

- The suicidality risks and, therefore, the need for the warnings, apply to any drug product with antidepressant *activity*, regardless of whether the drug is approved to treat depression. For example:

    - These warnings appeared in the labeling for Seroquel XR when that product was approved only for treating schizophrenia, an indication for which protection has expired.

    - The same boxed warning appears in the labeling of other drugs with antidepressant properties that are not approved for the treatment of depression.

        - Zyban (bupropion hydrochloride) bears the boxed warning but is approved only as an aid to smoking cessation treatment.
        - Sarafem (fluoxetine hydrochloride) bears the boxed warning but is approved only for the treatment of Premenstrual Dysphoric Disorder.
        - Anafranil (clomipramine) bears the warning but is approved only for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder.

The reasons above are also consistent with draft guidance issued by the agency. See Draft Guidance for Industry, *Suicidality: Prospective Assessment of Occurrence in Clinical Trials* (Sept. 2010) (Draft Guidance). FDA's current view, as articulated in the Draft Guidance, is that suicidality risks may be present and therefore should be evaluated for all drugs being developed for a psychiatric condition, not just those approved for depression indications, and some non-psychiatric drugs, such as tretinoins, beta blockers, smoking cessation and weight loss drugs, and antiepileptics. Therefore, the presence of a suicidality warning does not necessarily connote approval for a depression-related indication.

Moreover, as noted in the Draft Guidance, "There are no data to support the view that patients with nondepressed psychiatric disorders have any lesser vulnerability to treatment-induced suicidality than patients with overt depression. If anything, based on limited exploratory analyses of the adult antidepressant data, the risk may be greater in nondepressed psychiatric patients." Draft Guidance at 8.

For these reasons, the warnings at issue here are necessary for the safe use of generic quetiapine products referencing Seroquel, are not protected, and are consistent with agency guidance on the subject.

IV. CONCLUSION

In sum, FDA concurs that these portions of the labeling are essential to safe use of a generic quetiapine product referencing Seroquel for any indication, and the agency would not approve a quetiapine ANDA referencing Seroquel that omitted them. FDA does not concur, however, that

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supplement for monotherapy for the acute treatment of depressive episodes associated with bipolar I disorder. Seroquel's exclusivity for that bipolar indication has since expired. The warnings cannot become protected *post hoc*.

an ANDA referencing Seroquel is precluded from including Table 2 or the suicidality warnings by virtue of AstraZeneca's 3-year exclusivity on certain indications for Seroquel XR.

Sincerely,

Keith O. Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

cc: ANDA Sponsors

Appendix I: Section 5.2 Suicidality Warnings

5.2 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated**
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SEROQUEL is approved for use in treating adult bipolar depression.

Appendix 2: Trials Represented in Table 2

	Protocol Number	Patient Population/ Diagnostic Group	Drug(s)
1	D144C00132	Schizophrenia	Seroquel and Seroquel XR arms
2	D144C00133	Schizophrenia	
3	D147C00001	Bipolar depression	Seroquel
4	D147C00134	Bipolar disorder	
5	D147C00135	Bipolar depression	
6	D1448C00001	Major depressive disorder (MDD)	Seroquel XR
7	D1448C00002	MDD	
8	D1448C00003	MDD	
9	D1448C00004	MDD	
10	D1448C00008	Healthy volunteers	
11	D1448C00009	Generalized Anxiety Disorder (GAD)	
12	D1448C00010	GAD	
13	D1448C00011	GAD	
14	D144CC00002	Bipolar depression	
15	D144CC00004	Bipolar mania	

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/s/

KEITH O WEBBER
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