September 9, 2014

Division of Dockets Management
FOOD AND DRUG ADMINISTRATION
Department of Health and Human Services
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

CITIZEN PETITION

Dear Madam or Sir:

Otsuka Pharmaceutical Development & Commercialization, Inc., on behalf of its parent company, Otsuka Pharmaceutical Co., Ltd. ("Otsuka"), hereby submits this petition under section 505(q) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), in accordance with 21 C.F.R. § 10.30, to request that the Commissioner of Food and Drugs refuse to accept for substantive review a New Drug Application ("NDA") submitted by Alkermes plc ("Alkermes") for approval of aripiprazole lauroxil because the application, based on public representations by Alkermes, is deficient on its face.

Otsuka holds an approved NDA for Abilify® (aripiprazole), an atypical antipsychotic indicated for treatment of schizophrenia, and several other psychiatric indications. Otsuka also holds an approved NDA for Abilify Maintena® (aripiprazole), a long-acting formulation for treatment of schizophrenia. On August 25, 2014, Alkermes announced the submission of an NDA for aripiprazole lauroxil (the “Alkermes NDA”), which Alkermes proposes as a long-acting formulation for treatment of schizophrenia. Alkermes seeks FDA approval based only on results from a purported single adequate and well-controlled clinical trial (“AWCT”) of aripiprazole lauroxil despite the fact that aripiprazole lauroxil is a New Chemical Entity (“NCE”) according to an FDA bright-line rule, which establishes when an active moiety is deemed to be an NCE based on chemical structure.

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1 NDA No. 021436.
2 NDA No. 202971.
4 As used throughout this petition, a New Chemical Entity or NCE shall have the meaning set forth in 21 C.F.R. § 314.108(a), as interpreted and applied by FDA and as described below in Section II.b.
A. ACTION REQUESTED

Otsuka respectfully requests that FDA refuse to accept for substantive review the Alkermes NDA, seeking approval for a new active moiety not contained in any previously-approved drug product, because the single AWCT reported in the application cannot satisfy the substantial evidence of effectiveness requirement prescribed in Section 505(b)(1)(A) of the FFDCA.

B. STATEMENT OF GROUNDS

I. Summary of Argument

The Alkermes NDA should not be accepted for filing because it does not satisfy the information requirements of Section 505(b) and thus cannot be ultimately approved. Specifically, the Alkermes NDA is deficient on its face because it cannot meet the statutory requirement for demonstration of substantial evidence of effectiveness. First, FDA generally requires that NDAs provide evidence of effectiveness based on at least two AWCTs of the proposed drug product to ensure that the results are independently reproducible. However, the Alkermes NDA contains full reports of only a single, new AWCT of aripiprazole lauroxil.

Second, the Alkermes NDA does not meet any of FDA’s criteria for approving an NDA based on only a single new AWCT. FDA has approved NDAs with reports of a single AWCT of a new use of an already-approved drug. However, according to FDA’s bright-line rule, aripiprazole lauroxil is deemed to contain a new active moiety that has never been contained in a previously approved drug product. Consequently, the single study of aripiprazole lauroxil is the only available study of a drug with a new active moiety rather than a new use of an approved drug. In accordance with the applicable FDA rule, having only a single study is not sufficient in this case to trigger acceptance for substantive review.

FDA has also approved new drugs based on a single new AWCT of a drug with a new active moiety. However, FDA has narrowly limited this exception to proposed drug products with a single AWCT that have demonstrated certain types of effects (such as reduction in mortality) where it would be unethical to require a second, confirmatory study. The Alkermes NDA, according to Alkermes’s public statements, does not meet these criteria.

A decision that a single AWCT is sufficient to support approval of the Alkermes NDA in this instance would require an arbitrary and capricious break with prior precedent and a sharp departure from FDA’s well-established interpretations of relevant statutes and regulations. The present application does not warrant commitment of agency resources for a substantive review until the application is resubmitted with the legally necessary information as defined under the Act. Furthermore, this petition presents a clear legal question that does not require substantive scientific review for resolution. As described below, FDA can – and should – exercise its discretion to refuse to accept for substantive review the Alkermes NDA because no amount of substantive review can remedy the failure of the Alkermes NDA to meet applicable statutory and regulatory requirements.
II. Legal Background

a. Standard for Refusing to Accept Application For Review

FDA may refuse to accept an NDA for review if, among other reasons, the application “is incomplete because on its face it does not contain the information required under section 505(b).” According to FDA, this includes: “Failure to include evidence of effectiveness compatible with statute and regulations.” One such failure is: “Presentation of a single adequate and well-controlled trial without adequate justification of why the single trial should be regarded as fulfilling the statutory requirement for substantial evidence of effectiveness.”

According to FDA, “RTF [Refusal-to-file] is an important regulatory tool to help CDER avoid unnecessary review of incomplete applications,” because “[i]ncomplete applications can lead to multiple-cycle reviews and inefficient use of CDER resources.” Moreover, “CDER also believes an RTF action can allow an applicant to begin repair of critical deficiencies in the application far sooner than if these were identified much later in a complete response action and may lead to more rapid approval of safe and effective drug products.” Consequently, substantive review of a deficient application would be a waste of time and resources for both the agency and the applicant.

b. Standard for Distinguishing New Active Moieties

FDA defines an NCE as “a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.” An active moiety is defined, in turn, as:

[T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other non-covalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

According to this bright-line definition of active moiety, NCE status is determined exclusively on the basis of chemical structure rather than on a case-by-case analysis of pharmacological activity. Thus, “an ester, salt . . . , or other noncovalent derivative . . . of [a] molecule” is deemed to be the same molecule (and thus same active moiety), whereas a molecule with a non-ester covalent bond is deemed to be a different molecule (and thus a new active moiety) – “even if the

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5 21 C.F.R. § 314.101(d)(3).
7 Id.
8 Id., at 2.
9 Id.
10 21 C.F.R. § 314.108(a).
11 Id.
molecule includes a covalent bond to a molecule that was itself previously an active moiety."\textsuperscript{12} In sum, "[i]f the drug substance is composed of non-ester covalently bonded molecules, the covalently bonded molecule is considered the active moiety."\textsuperscript{13} 

FDA has provided the following scientific justification for its bright-line rule that treats covalent structural changes to a molecule as an NCE:

[I]t has been FDA’s longstanding experience that even minor covalent structural changes are capable of producing not only major changes in the activity of the drug but changes that are not readily predicted. Because of their potential significance, FDA has always identified changes in covalent structure, including minor changes ... as sufficient to create a new “active moiety,” and thereby to create a new chemical entity.

The potential significance of modifications in covalent structure, even where previously approved drugs contain the same “active site,” is reflected in the amount and kind of data required for approval of such changes. Such a change requires submission of an amount of data comparable to that required for an entirely new molecule.\textsuperscript{14}

FDA provides the following justification for treating the formation of a salt or ester of a molecule, or other non-covalent changes to a molecule, as the same active moiety:

In contrast to most changes in the covalent structure of a molecule, the formation of a salt or a complex, or of an ester, is not intended to, and generally cannot, alter the basic pharmacologic or toxicologic properties of the molecule.\textsuperscript{15}

c. Standard for Demonstrating Clinical Safety and Effectiveness

NDA sponsors must submit “full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use.”\textsuperscript{16} Section 505(b)(1)(A) contemplates that the required reports of investigations of safety and effectiveness supporting the approval of “such drug” will have been conducted by the sponsor or by another entity from whom the sponsor has obtained a right of reference. In contrast, Section 505(b)(2) makes reference to “an application ... for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not

\textsuperscript{12} Letter from Gary J. Buehler, Office of Generic Drugs, FDA, to Chad A. Landmon (Oct. 23, 2009) (hereinafter "Vyvanse Citizen Petition Response"), at 12.
\textsuperscript{13} Id., at 11.
\textsuperscript{14} Id. at 14 (quoting a July 26, 1989, Citizen Petition Response, Docket No. 1987P-0339, at 11-12).
\textsuperscript{15} Id.
\textsuperscript{16} FFDCA § 505(b)(1)(A). Although the term “such drug” is not precisely defined in section 505(b), it refers to the particular “drug product” for which approval is sought (i.e., a finished dosage form (such as a tablet or capsule)) that contains an active ingredient “intended to furnish pharmacological activity or other direct effect” on the human body, 21 C.F.R. § 314.3(b). It is clear from a plain reading of the statute that the antecedent of the term “such drug” in 505(b)(1)(A) is the term “any drug” in 505(b)(1) for which an application is filed.
conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." Under section 505(b)(2), the source of the “full reports of investigations” may differ from that contemplated under section 505(b)(1). However, in both cases, the quantity and quality of the required investigations of safety and effectiveness must meet the statutory standards of section 505(b)(1)(A).

FDA shall not approve an application submitted under 505(b) if the investigations required under 505(b)(1)(A) are inadequate to support a finding of safety, or provide evidence that the proposed drug is not safe. Section 505(d)(5) of the FFDCA also establishes a “substantial evidence” standard for determining whether “such drug . . . will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.” If these tests of safety and effectiveness are not met, the NDA cannot be approved.

The “substantial evidence” standard for demonstrating effectiveness has been defined as “adequate and well-controlled investigations” to enable qualified experts to conclude “that the drug will have the effect it purports.” The phrase “adequate and well-controlled investigations” has generally been interpreted to mean at least two individual adequate and well-controlled human clinical trials, which FDA has deemed necessary to satisfy a basic principle of scientific investigations by ensuring that clinical trial results are reproducible.

Although the “substantial evidence” approval standard generally requires at least two well-controlled clinical trials, a 1997 amendment to section 505(d) provides that “data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation)” may constitute “substantial evidence” of effectiveness in some cases. According to FDA, this statutory amendment merely confirmed prior FDA practice: “In making this clarification, Congress confirmed FDA’s interpretation of the statutory requirements for approval and acknowledged the Agency’s position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.”

FDA has consistently identified only two circumstances in which a single, new AWCT may be sufficient to show “substantial evidence” of effectiveness. The first is where “a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness.” In other words, evidence from one or more AWCTs of a

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17 FFDCA § 505(b)(2).
18 FFDCA § 505(d)(1)-(4).
19 FFDCA § 505(d)(5).
20 FFDCA § 505(d)(7).
21 See, e.g., Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998, (hereinafter “Clinical Effectiveness Guidance”) at 4 (“The usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness.”).
23 Clinical Effectiveness Guidance, at 4.
24 See generally Clinical Effectiveness Guidance.
25 Id., at 8.
previously-approved drug product with the same active moiety can count toward the two-study requirement for a proposed new use of that same active moiety (e.g., in a different dosage form). The second is where a single AWCT meets one or more factors related to the size of the study, multiple endpoints, consistent results across population subsets, and strength of statistical results (i.e., large and complex trials that provide a level of evidence comparable to two or more independent studies). However, FDA has stated that this second exception “will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.”

d. Demonstrating Safety and Effectiveness of NCEs Under Section 505(b)(2)

FDA distinguishes between applications that are submitted under Section 505(b)(2) as a modification to a previously approved drug and those submitted as an NCE. For an application seeking approval of a modification to a previously approved drug, the sponsor may rely, in part, on FDA’s finding of safety and effectiveness of the previously approved product, “coupled with the information needed to support the change from the approved product.” In other words, reliance on previously-approved NDAs to support a finding of safety and effectiveness is appropriate where the new drug product and reference drug product contain the same active moieties.

Although an NCE may also be approved under Section 505(b)(2), FDA states that data to support such an application “is likely to be derived from published studies, rather than FDA’s previous finding of safety and effectiveness of a drug.” This reference to use of supporting literature is based on the potential that an NCE “may have been studied by parties other than the applicant and published information may be pertinent to the new application.” An NCE would thus be suitable for approval under Section 505(b)(2) when it is based on independent published studies rather than prior FDA findings of effectiveness because the required investigations must be evaluations of the active moiety contained in the proposed new drug product.

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26 Id., at 7-12.
27 Id., at 12-16.
28 Id., at 13.
30 505(b)(2) Draft Guidance, at 3.
31 Id.
32 Id., at 5.
33 The 505(b)(2) Draft Guidance also includes a general statement that “[i]n some cases, data on a drug with similar pharmacologic effects could be considered critical to approval.” 505(b)(2) Draft Guidance, at 5. The Draft Guidance does not elaborate further on the circumstances in which such data may be relied upon, nor on what the definition of critical is in this context. However, the potential relevance of information from another drug product with a different active moiety than is contained in the proposed drug product does not change the default
III. Factual Background

Otsuka holds an NDA for Abilify (aripiprazole), an atypical antipsychotic initially approved in tablet form by FDA on November 15, 2002, for the treatment of schizophrenia. Subsequent to the initial approval, FDA has approved multiple new applications for different formulations, dosage forms and routes of administration of Abilify, as well as several additional indications for the product. Most recently, on February 28, 2013, FDA approved an NDA for Abilify Maintena (aripiprazole), a long-acting, intra-muscular injection for the treatment of schizophrenia.

Each of the approved formulations and dosage forms of Abilify, including Abilify Maintena, is based on the same active moiety, aripiprazole, the chemical structure of which is depicted in Figure 1.

On August 25, 2014, Alkermes announced that it had submitted to FDA an NDA seeking approval of a compound called aripiprazole lauroxil, a “once-monthly, long-acting injectable atypical antipsychotic for the treatment of schizophrenia.” The chemical structure of aripiprazole lauroxil is depicted in Figure 2.

According to Alkermes “[o]nce in the body, aripiprazole lauroxil converts to aripiprazole, which is commercially available under the name ABILIFY®.” However, this conversion process produces an intermediate molecule, N-hydroxymethyl aripiprazole. According to Alkermes:

Conversion of aripiprazole lauroxil to aripiprazole after administration is governed by a process, which involves dissolution of the prodrug from the injection site, subsequent enzyme-mediated cleavage that generates an intermediate form (N-hydroxymethyl aripiprazole), and dissociation of a covalently bonded hydroxymethyl group that ultimately results in release of the aripiprazole active moiety.

The chemical structure of the intermediate form, N-hydroxymethyl aripiprazole is depicted in Figure 3.
Figure 1: Abilify (aripiprazole) and Abilify Maintena (aripiprazole)

Figure 2: Aripiprazole Lauroxil

Figure 3: N-Hydroxymethyl aripiprazole
Alkermes seeks FDA approval based only on results from a single AWCT—“the pivotal phase 3 study assessing the efficacy and safety of aripiprazole lauroxil, in which aripiprazole lauroxil demonstrated significant improvements in schizophrenia symptoms, compared to placebo.”

There are no independent published literature reports of studies of aripiprazole lauroxil that support a finding that aripiprazole lauroxil is safe and effective.

IV. Discussion

Alkermes seeks approval for an NCE supported by a single AWCT without adequate justification for submitting results from a single AWCT. Because the Alkermes NDA does not—and cannot—satisfy the information requirements of Section 505(b), the application should not be accepted for substantive review.

a. The aripiprazole lauroxil NDA must contain reports from at least two AWCTs of the proposed active moiety unless it meets established exceptions permitting only a single new AWCT

FDA has established a bright-line rule, based exclusively on chemical structure, for defining whether the active moiety of a prodrug such as aripiprazole lauroxil is the whole molecule (i.e. aripiprazole lauroxil) prior to the bioconversion process or the previously-approved molecule ultimately released through a bioconversion process (i.e. aripiprazole). Under FDA’s bright-line rule, it is irrelevant that aripiprazole lauroxil “ultimately” “convert[s]” into aripiprazole when determining whether the active moiety is aripiprazole lauroxil or aripiprazole. The deciding factor is the chemical structure prior to bioconversion, and, specifically, whether there are covalent structural modifications. The chemical structures of Abilify (aripiprazole) and aripiprazole lauroxil, as depicted in Figures 1 and 2, respectively, are not identical. Aripiprazole lauroxil consists of the aripiprazole moiety with a covalently bonded lauroxil group, which makes aripiprazole lauroxil an NCE under FDA’s bright-line rule.

Alkermes suggests that aripiprazole lauroxil is essentially the same drug as aripiprazole because aripiprazole lauroxil undergoes a conversion process “that ultimately results in release of the aripiprazole active moiety.” However, Alkermes also acknowledges that the conversion process includes “enzyme-mediated cleavage that generates an intermediate form (N-hydroxymethyl aripiprazole), and dissociation of a covalently bonded hydroxymethyl group.” These two statements suggest that Alkermes is trying to benefit from both sides of FDA’s bright-line rule.

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41 Alkermes Poster, June 17, 2014.
43 Alkermes Poster, June 17, 2014.
44 Id.
On one hand, Alkermes’s published reference to “dissociation of a covalently bonded hydroxymethyl group” squarely and unequivocally places aripiprazole lauroxil on one side of FDA’s bright-line rule as an active moiety that is not the same as aripiprazole. In fact, Alkermes’s acknowledgment of an intermediate produced during the bioconversion process, which published data suggest may remain present for extended periods following administration, is consistent with the rationale FDA has provided for its bright-line rule regarding covalently-bonded molecules. On the other hand, Alkermes’s published reference to release of “the aripiprazole active moiety” from aripiprazole lauroxil suggests that aripiprazole and aripiprazole lauroxil contain the same active moiety. Alkermes apparently tries to use this representation to justify its submission of results from only a single AWCT and dependence on FDA’s findings of safety and effectiveness of Abilify to support approval of aripiprazole lauroxil. Alkermes cannot have it both ways, and FDA should not permit Alkermes to treat aripiprazole lauroxil selectively as the same active moiety as aripiprazole and a new active moiety when FDA has established a bright-line rule.

2. As a matter of established law, an NDA for an NCE must generally contain full reports of two clinical trials

Section 505(b) of the FFDCA requires that NDAs must contain full reports of “investigations” sufficient to establish the effectiveness of an NCE. FDA has long, and consistently, interpreted this provision to require at least two adequate and well-controlled clinical trials to establish “substantial evidence” of effectiveness except where limited exceptions are satisfied. FDA


46 See supra notes 13-15 and accompanying text.

47 See, e.g., Richard Pops, Chairman and CEO, Alkermes’s CEO Presents at Goldman Sachs Healthcare Conference Transcript (June 11, 2013), available at http://seekingalpha.com/article/1500922-alkermes-ceo-presents-at-goldman-sachs-healthcare-conference-transcript (“What [sic] so, cool about Aripiprazole Lauroxil, 9070 is that, because the active moiety is aripiprazole. We inject this once a month into the muscle as a prodrug, it metabolizes into aripiprazole, we track in the blood stream aripiprazole levels . . . . We know that we’re delivering therapeutic concentrations of aripiprazole.”); Richard Pops, Chairman and CEO, Alkermes CEP Presents at Citi Global Healthcare Conference Transcript (Feb. 25, 2013), available at http://seekingalpha.com/article/1222541-alkermes-ceo-presents-at-citi-global-healthcare-conference-transcript (“Once in the body this more complicated molecule antibody clips down to Aripiprazole, for the active moiety in the blood stream of these patients for the month and time is Aripiprazole, and that way we can build off of a huge clinical foundation of safety and efficacy of this molecule.”); Jim Frates, Senior VP and CFO, Alkermes’s Management Presents at Deutsche Bank 38th Annual dbAccess Health Care Conference Transcript (May 29, 2013), available at http://seekingalpha.com/article/1467941-alkermes-management-presents-at-deutsche-bank-38th-annual-dbanaccess-health-care-conference-transcript (“[W]hat we are trying to do is deliver Aripiprazole, native Aripiprazole, over the course of a month.”); Richard Pops, Chairman and CEO, Alkermes’s CEO Presents at Bank of America Merrill Lynch Smid Cap Conference Transcript (May 8, 2013), available at http://seekingalpha.com/article/1415361-alkermes-ceo-presents-at-bank-of-america-merrill-lynch-smid-cap-conference-transcript (“Our product is a prodrug, the prodrug of Aripiprazole designed specifically to be an injectable product once a month. Once it’s injected, it fits comfortably in the muscle for a long period of time and it tubulizes and releases Aripiprazole.”); James Frates, CFO, Alkermes’ Management Presents at Credit Suisse 2012 Healthcare Conference Transcript (Nov. 14, 2012), available at http://seekingalpha.com/article/1009251-alkermes-management-presents-at-credit-suisse-2012-healthcare-conference-transcript (“And one of the things – one of the questions we don’t have to answer in the clinical program is whether ABILIFY actually treats schizophrenia.”).

48 See generally, Clinical Effectiveness Guidance.
Guidance states that “it has been FDA’s position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness” for a new drug. 49

The text of the FFDCA and FDA’s regulations make it clear that the investigations required to demonstrate substantial evidence of effectiveness must be investigations of the proposed new drug. While FDA generally defines “drug” to mean a particular “drug product,” i.e., a specific formulation of a product containing one or more active ingredients, investigation of a particular drug product necessarily requires investigation of the active moiety contained in the proposed new drug product. Put simply, the default two-study rule to demonstrate clinical effectiveness cannot be satisfied by evidence from the findings of effectiveness for a drug product containing an active moiety that is not contained in the proposed new drug. 50

Alkermes appears to recognize that its application, with reports of only a single AWCT of aripiprazole lauroxil, is inadequate to support approval under Section 505(b) based only on data from its own application. This fact is evidenced by Alkermes’s acknowledgment that approval of its application depends on additional data from clinical trials supporting the Abilify label. 51 However, clinical trials evaluating the effectiveness of Abilify cannot simply be deemed by Alkermes to represent a clinical trial of the same active moiety as that contained in aripiprazole lauroxil when FDA’s bright-line rule clearly establishes that aripiprazole lauroxil contains a different active moiety than Abilify. Neither prior studies of Abilify nor any other published studies apart from Alkermes’s single trial provide any clinical data showing the effectiveness of aripiprazole lauroxil and its intermediate form, N-hydroxymethyl aripiprazole. Therefore, there are no external data that Alkermes can use to satisfy the general rule requiring at least two clinical investigations of the proposed new drug.

49 Id., at 2.
50 This conclusion is consistent with FDA’s guidance on the necessary evidence to demonstrate clinical effectiveness. As reviewed below, infra note 53 and accompanying text, one exception to the two-study rule is where studies of other formulations involving the same active moiety can be used to support approval based only on a single new AWCT of the proposed new drug product. This suitability of using evidence from another drug product containing the same active moiety as a proposed new drug product underscores the fact that the investigations to show substantial evidence of effectiveness must be conducted on the active moiety contained in the proposed new drug product. It is also consistent with FDA’s justification for treating covalently bonded molecules as NCEs, which are then treated as requiring “submission of an amount of data comparable to that required for an entirely new molecule.” Vyvanse Citizen Petition Response, at 12.
51 See, e.g., Richard Pops, Chairman and CEO, Alkermes CEP Presents at Citi Global Healthcare Conference Transcript (Feb. 25, 2013), available at http://seekingalpha.com/article/1222541-alkermes-ceo-presents-at-citi-global-healthcare-conference-transcript (“Once in the body this more complicated molecule antibody clips down to Aripiprazole, for the active moiety in the blood stream of these patients for the month and time is Aripiprazole, and that way we can build off of a huge clinical foundation of safety and efficacy of this molecule.”).
b. The Alkermes NDA does not meet either of the two exceptions that would permit approval on the basis of a single AWCT

1. Aripiprazole lauroxil is not a new use of an active moiety contained in a previously approved drug product

It is well established that “a single study of a new use” of a previously approved drug product can provide evidence of effectiveness. However, this exception to the general rule requiring two new studies depends on availability of “independent substantiation from study data in related uses” of the same active moiety. In such cases, at least two clinical trials have been conducted on the relevant active moiety (thereby satisfying the underlying concern about reproducibility) even though only a single study was conducted for the proposed new use of a previously approved active moiety. Such was the case with Abilify Maintena. Only a single new AWCT was conducted to support approval of Abilify Maintena. However, taken together with multiple AWCTs of Abilify, which contains the exact same active moiety as Abilify Maintena, multiple AWCTs supported the approval of Abilify Maintena.

Because aripiprazole lauroxil is deemed to be a new active moiety rather than a new use of the same active moiety in a previously approved drug, there is no available “independent substantiation” of the effectiveness of aripiprazole lauroxil based on previously-approved drug products. Consequently, the first exception to the two-trial default rule cannot be applicable to aripiprazole lauroxil.

2. The single AWCT of aripiprazole lauroxil demonstrated symptomatic benefit rather than reduced morbidity/mortality or prevention of disease where repetition of trial results would pose ethical concerns

The second exception to the default two-trial rule is reserved for a large, well-designed study with strong statistical results that provides evidence of effectiveness comparable to two or more

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52 See Clinical Effectiveness Guidance, at 8 (emphasis added). See generally Clinical Effectiveness Guidance, 8-12.
53 Id., at 8.
54 Although an NCE that contains a covalently bonded chain to the active moiety of a previously approved drug may be considered “related” to that drug, prior precedent indicates that drug products satisfying the bright-line rule for an NCE are required to conduct at least two clinical studies to show effectiveness. See, e.g., the NDAs for Vyvanse (NDA No. 021977), Colazal (NDA No. 020610), Cerebyx (NDA No. 020450), Lusedra (NDA No. 022244), and Neurontin (NDA No. 020235). In one case FDA approved an NDA for a prodrug with a covalent bond without requiring two AWCTs. However, in that case FDA later conceded it had erred in failing to classify Emend as an NCE, leaving open the question of what FDA would have required at the time of approval if Emend was properly classified as an NCE. See Memorandum from Gary Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to NDA 022023 – Emend for Injection, Merck and Co. Inc., Emend Exclusivity Determination (Dec. 1, 2009) (“Emend for Injection under FDA’s interpretation of 21 CFR § 314.108 should have been classified as the time of approval as an NCE.”), available at http://www.accessdata.fda.gov/drugsatfda_docs/NDA/2008/022023s000_AdminCorres_P2.pdf.
55 As contemplated by FDA’s 505(b)(2) guidance, it might be possible that an NCE could be approved under 505(b)(2) if there was independent published data regarding the new active moiety. 505(b)(2) Draft Guidance, at 3, 5. However, there have not been any other clinical trials of aripiprazole lauroxil independently reported in published literature.
trials (thereby satisfying the underlying concern about reproducibility). However, this exception will “generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.” FDA has been consistent in limiting approvals of NCEs based on reports of a single AWCT to NDAs that meet these strict criteria.

Nothing in Alkermes’s public statements suggests that Alkermes believes it meets this strict standard. Alkermes claims only that its single AWCT of aripiprazole lauroxil demonstrated symptomatic improvement from baseline— not a clinically meaningful effect on mortality or irreversible morbidity. Nor has Alkermes suggested that there might be an ethical consideration to prevent a second clinical trial. Thus, confirmation of the first trial’s result in a second trial is not “practically or ethically impossible.” Accordingly, there is no basis for Alkermes to contend that a single AWCT is sufficient to provide “substantial evidence” of effectiveness.

c. FDA should not accept for substantive review an NDA that is deficient on its face and cannot be approved without resubmission of the NDA

FDA has ample authority to refuse to accept for filing an NDA if, among other things, it “is incomplete because it does not on its face contain information required under section 505(b).” Because the Alkermes NDA is based on a single AWCT of aripiprazole lauroxil, and because aripiprazole lauroxil is deemed to be an NCE under FDA’s bright-line rule, the Alkermes NDA is deficient on its face and, thus, cannot be approved in its present form. The deficiencies in the

56 Clinical Effectiveness Guidance, at 13.
57 See, e.g., the NDAs for Brilinta (NDA No. 022433) (indicated for the reduction of thrombotic cardiovascular events in patients with acute coronary syndrome based on one very large adequate and well-controlled clinical trial); Jevtana (NDA No. 201023) (indicated in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen, a patient population without any treatment options offering a survival benefit); Folotyn (NDA No. 022468) (indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma, a patient population without any approved treatment options); Tyzeka (NDA No. 022011) (indicated for the treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation based on one trial that was designed to be effectively two trials in one); and Iplex (NDA No. 021884) (indicated for the treatment of the extremely rare condition of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone).
58 Alkermes Poster, June 17, 2014 (“The primary outcome measure is the change from baseline to Day 85 in the Positive and Negative Syndrome Scale (PANSS) total score.”). As FDA has clearly stated, “[r]epetition of positive trials showing only a symptomatic benefit would generally not present the same ethical concerns” as a drug showing a clinically meaningful effect on mortality or irreversible morbidity, and this weighs strongly in the “matter of judgment” of the review staff. Clinical Effectiveness Guidance, at 13.
59 Such a claim would be dubious given the current market availability of Abilify Maintena, the ability for Alkermes to conduct an active control trial against Abilify Maintena, and the fact that Alkermes chose to conduct a placebo study for its trial.
60 Clinical Effectiveness Guidance, at 13.
61 21 C.F.R. § 314.101(d)(3)
Alkermes aripiprazole lauroxil NDA cannot be resolved during the review cycle because a second trial is required under applicable law and regulation. Moreover, the necessity to conduct a second trial on aripiprazole lauroxil presents a legal question that does not require scientific expertise to substantiate an agency final decision. Therefore, substantive review of the application as submitted would be a waste of time and agency resources.

2. Substantive review of the Alkermes NDA is inappropriate because approval of aripiprazole lauroxil based on a single AWCT would be an arbitrary and capricious departure from agency policy.

An RTF decision is particularly warranted in the case of the aripiprazole lauroxil NDA because, for all of the reasons discussed above, there is no reasonable basis upon which FDA could ultimately approve the NDA following a complete review. As submitted, the Alkermes NDA could only be approved with data from a single AWCT involving an active moiety never before contained in an approved drug product. Such an approval of aripiprazole lauroxil on a single AWCT would upend the “delicate balance” enshrined in the Hatch/Waxman amendments.

Section 505(b)(2), under which Alkermes appears to seek an abbreviated approval, was part of an attempt to balance the importance of innovation (through grants of exclusive marketing rights) and lower-cost generic drugs (supported by abbreviated approval pathways enabling sponsors to rely on FDA findings of safety and effectiveness of approved drug products and thus avoid conducting AWCTs). 62

Alkermes essentially wants to be considered the same as Abilify to avail itself of an abbreviated pathway reserved for drug products with the same active moiety and yet different than Abilify to obtain five years of marketing exclusivity reserved for NCEs. According to Alkermes, “the molecule we have developed is a new chemical entity called aripiprazole lauroxil,” 63 which would thus be expected to qualify for five years of FDA marketing exclusivity granted to all NCEs. 64 However, Alkermes also claims that, because of the ultimate conversion into the aripiprazole moiety, aripiprazole lauroxil is essentially the same drug, treating the same patient population, for the same indication(s), with the same expected clinical benefit as Abilify, and

62 Public statements by Alkermes suggest that Alkermes is poised to market aripiprazole as a high-value brand drug, rather than as a low-cost generic copy of the previously-approved drug product, Abilify. See, e.g., Mark Stejbach, Chief Commercial Officer, Alkermes Plc CEO Hosts R&D Day Transcript (July 17, 2013), available at http://seekingalpha.com/article/1557512-alkermes-plc-alks-ceo-hosts-r-and-d-day-transcript?part= single (“If you are going to pick a next one – and Aripiprazole obviously is the next one with Maintena recently being approved – it makes sense as the market leader. So, this is sales on a world-wide basis. This is all indication, so a big market. But the point here is Abilify is a $7 billion drug; it’s the market leader . . . If you look at Abilify Maintena, what this tells you is, this is still a premium product market. It is not a matter of price cutting to gain share in a commodity-like market.”). Approval of aripiprazole lauroxil would, therefore, not further the Hatch/Waxman purpose of supporting lower-cost generic drugs.


64 See, e.g., Memorandum from Gary Buehler, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to NDA 022023 – Emend for Injection, Merck and Co. Inc., Emend Exclusivity Determination (Dec. 1, 2009) (indicating that a prodrug that includes a covalent bond should be awarded five-year exclusivity as an NCE despite the speed with which it is converted to a previously-approved active moiety after administration), available at http://www.accessdata.fda.gov/drugsatfda_docs/NDA/2008/022023s000_AdminCorres_P2.pdf.
that the safety and effectiveness of aripiprazole lauroxil can therefore be supported by FDA’s findings regarding Abilify (aripiprazole). Drug sponsors should not be able to have it both ways. FDA appears to recognize that this type of outcome cannot be countenanced.

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**d. If accepted for substantive review, the Alkermes NDA must be denied**

This petition formally requests only that FDA refuse to file the Alkermes NDA. However, in the event that FDA accepts the Alkermes NDA for filing and thereby implicitly denies this citizen petition, the Alkermes NDA must not be approved for all of the reasons reviewed herein, which are incorporated here by reference.

**e. Conclusion**

For the reasons, and on the basis of the legal authority, cited above, FDA should grant Otsuka’s request that the agency refuse to accept for substantive review the NDA submitted by Alkermes for aripiprazole lauroxil, an acknowledged NCE under the FDA’s bright-line rule, because the single AWCT upon which the NDA is based is not sufficient to provide “substantial evidence of effectiveness” for the proposed indication, as required by Section 505(b)(1)(A).

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**C. ENVIRONMENTAL IMPACT**

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

**D. ECONOMIC IMPACT**

Petitioner will, upon request by the Commissioner, submit economic impact information in accordance with 21 C.F.R. § 10.30(b).

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65 *See supra* note 47.

66 *See, e.g.*, Consolidated 505(b)(2) Response, at 34 (“FDA is particularly interested in examining the use of 505(b)(2) applications to obtain approval of drug products for which the only difference from the listed drug is in the form of the active ingredient, such as a change in salt . . . . This use of section 505(b)(2) does not result in the approval of an innovative drug product that offers a new therapeutic benefit or alternative . . . . In this way or do such changes in the active ingredient generally represent an improvement in terms of safety or effectiveness. FDA is concerned that, in addition to not representing innovating drug development, this use of 505(b)(2) applications may have undesirable policy and public health consequences:

1. It may undermine current incentives for development of promising new active moieties that Congress included in the Hatch-Waxman Amendments.

2. It may lead to proliferation of pharmaceutical alternative drug products, with resulting confusion in the marketplace.

3. It may divert resources, otherwise available for innovative drug research, to the development and patenting of alternative active ingredients”).
E. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following dates: July 26, 2012 (Alkermes announcement of initiation of Phase 3 clinical trial of aripiprazole lauroxil) and August 25, 2014 (Alkermes announcement of submission of NDA to FDA based on single Phase 3 clinical trial). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Otsuka Pharmaceutical Development & Commercialization, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

OTSUKA PHARMACEUTICAL CO, LTD.

By: William H. Carson, M.D.
President & CEO
Otsuka Pharmaceutical Development & Commercialization, Inc.

Cc: Elizabeth H. Dickinson, Esq., Chief Counsel to the FDA
Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA
Exhibit A
Safety and Efficacy of Armodipine Lauroxil: Results from a Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study in Patients with Acute Exacerbation of Schizophrenia

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ABSTRACT

Background: Armodipine lauroxil (LAU), a novel, extended-release formulation of armodipine lauroxil (LAU), is a dihydropyridine calcium channel blocker that has been shown to improve the efficacy and tolerability of LAU in treatment-resistant schizophrenia patients when compared to placebo. The current study evaluated the safety and tolerance of 240 mg LAU over 4 weeks in patients with acute exacerbation of schizophrenia.

METHODS (cont’d)

RESULTS (cont’d)

• The primary endpoint was efficacy, as assessed by change from baseline in PANSS total score. The primary end point was analyzed using an analysis of covariance (ANCOVA) model with treatment as a random effect and baseline total PANSS score as a covariate.

• The results of this study support the conclusion that armodipine lauroxil may represent a new treatment option for patients with schizophrenia.

• The risks of this study are the evaluation of efficacy, safety, and tolerability of armodipine lauroxil in patients with acute exacerbation of schizophrenia.

Figure 3A. Change from Baseline in PANSS Total Score by Visit, ANCOVA LOCF

Figure 3B. Change from Baseline in PANSS Total Score by Visit, MMRM

• Statistically and clinically significant improvements with both doses of armodipine lauroxil were demonstrated as early as Day 8 and continued through Day 29.

• Both doses of armodipine lauroxil were well-tolerated overall.

REFERENCES


DISCLOSURES

This study was funded and conducted by Alkermes, Inc. All authors are employees of Alkermes, Inc.