DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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APR 30 2014

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Re: FDA-2013-P-0884, FDA-2013-P-1397

Dear Mr. Waxman and Ms. Fritz,

This is a combined response to two citizen petitions (collectively, Petitions) that ask the Food and Drug Administration (FDA or the Agency) to determine that, for a drug containing a new chemical entity (NCE) that requires scheduling under the Controlled Substances Act (CSA) by the Drug Enforcement Administration (DEA), the date of approval that starts the 5-year NCE exclusivity period under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and its implementing regulations is the date the new drug application (NDA) holder can commercially market the drug in interstate commerce.

The Petitions were submitted by two pharmaceutical companies (Petitioners), which market drugs containing NCEs that required scheduling. Eisai Inc. (Eisai) is the NDA holder of Fycompa (perampanel) (NDA 202834) and is marketing Belviq (lorcaserin hydrochloride) (NDA 022529). UCB, Inc. (UCB) is the NDA holder of Vimpat (lacosamide) (NDA 022253 and NDA 022254). Each of perampanel, lorcaserin, and lacosamide was an NCE at the time of its approval, and thus, was eligible for 5-year NCE exclusivity that began on the date of approval. Each drug also demonstrated the potential for abuse during the Agency's review of the NDA, and therefore, FDA recommended that each drug be scheduled by DEA.

Petitioners state that, under FDA's policy, a company cannot market its drug product containing an NCE that requires scheduling until DEA's scheduling is effective. Because DEA's scheduling becomes effective typically after the drug is approved, and thus after the 5-year NCE exclusivity period begins, Petitioners contend that they were not able to market their products without potential competition for the full 5 years.

We have carefully considered the information submitted in the Petitions and in comments submitted to the Petitions' dockets.[1] For the reasons described below, we are denying the Petitions.

I. BACKGROUND

A. Statutory and Regulatory Background

i. New Drug Applications and Abbreviated New Drug Applications

Section 505(b) of the FD&C Act establishes the approval requirements for NDAs. To be approved, an NDA submitted under section 505(b) must, among other things, be supported by investigations showing the drug product to be safe and effective.[2] One pathway under section 505(b) of the FD&C Act provides for approval of NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference (a 505(b)(1) application). The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) provided an alternate pathway under section 505(b)(2) of the FD&C Act for approval of an NDA for which some or all of the safety and efficacy investigations relied upon for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (a 505(b)(2) application). Like a 505(b)(1) application, a 505(b)(2) application is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act.

The Hatch-Waxman Amendments also provided for submission of abbreviated new drug applications (ANDAs) for approval of generic versions of listed drugs.[3] A *listed drug* is a drug product listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book)[4] with an effective approval under section 505(c) of the FD&C Act.[5] A *reference listed drug* (RLD) is the listed drug identified by FDA as the drug product on which an ANDA applicant relies in seeking approval of its application.[6] The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for an RLD rather than requiring the ANDA applicant to repeat the studies conducted to support approval of

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[1] Two comments were submitted to the Eisai's docket. One comment submitted on February 12, 2014, apparently from the applicant for Alfaxan, an animal drug, supported Eisai's assertions and noted that there have been significant delays with respect to DEA scheduling of that product. A second comment submitted on March 10, 2014, by the Pharmaceutical Research and Manufacturers of America (PhRMA), a trade association (hereafter, PhRMA comment), supported granting Eisai's Petition. One comment was submitted to UCB's docket. This comment was submitted on February 14, 2014, by Axinn, Veltrop & Harkrider LLP, on behalf of Hetero USA Inc. (hereafter Hetero comment), which asked FDA to deny UCB's petition.

[2] Section 505(b)(1) of the FD&C Act.

[3] Section 505(j) of the FD&C Act.

[4] The electronic version of the Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[5] 21 CFR 314.3(b).

[6] Id.

the RLD. To rely on such a finding, the ANDA applicant must show that, among other things, its proposed drug product is the same as the listed drug with respect to active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling, and that its product is bioequivalent to the RLD.[7]

ii. Approval Standards for New Drug Applications

Section 505(c)(1)(A) of the FD&C Act states that FDA shall "approve an application if [FDA] ... finds that none of the grounds for denying approval specified in [section 505(d) of the FD&C Act] applies." Section 505(d) of the FD&C Act includes the grounds for refusing to approve an application.

The FD&C Act recognizes two types of approvals for an NDA approved under section 505(c): (1) an "approval," which indicates that the application has met the statutory approval requirements under section 505(b) of the FD&C Act and none of the bases set out in section 505(d) of the FD&C Act are present (applicable to NDAs approved under both section 505(b)(1) and 505(b)(2) of the FD&C Act); and (2) a "tentative approval" (applicable to NDAs approved under only section 505(b)(2)). Tentative approval is defined in section 505(j)(5)(B)(iv)(II)(dd) of the FD&C Act as:

> notification to an applicant by [FDA] that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval because the application does not meet the requirements of this subparagraph [i.e., there are delays in approval related to patents or patent challenges], there is a period of exclusivity for the listed drug under subparagraph (F) or section 355a of this title, or there is a 7-year period of exclusivity for the listed drug under section 360cc of this title.

Although the FD&C Act defines tentative approval in the context of an ANDA, the Agency's regulations permit it to issue a tentative approval letter to applications submitted under section 505(b)(2) of the FD&C Act if the elements set forth in the statutory definition of tentative approval are met.[8]

FDA's regulations state that it "will approve an application and send the applicant an approval letter if none of the reasons in [21 CFR] 314.125 for refusing to approve the application applies."[9] This regulation also identifies the approval date of an NDA:

> An approval becomes effective on the date of the issuance of the approval letter, except with regard to an approval under section 505(b)(2) of the act with a delayed effective date. An approval with a delayed effective date is tentative and does not become final

[7] Section 505(j)(2) of the FD&C Act. Limited deviations from this sameness requirement may be permitted upon approval by FDA of a suitability petition. See Section 505(j)(2)(C) of the FD&C Act.

[8] See generally, 21 CFR 314.105(a), 314.107.

[9] 21 CFR 314.105(a).

> until the effective date. A new drug product or antibiotic approved under this paragraph may not be marketed until an approval is effective.[10]

FDA lists reasons to disapprove an application in 21 CFR 314.125(b), and these reasons generally track the statutory bases for refusing to approve an NDA found in section 505(d) of the FD&C Act.

In the regulations, FDA also addresses when the Agency will approve a product on the basis of draft labeling, providing that:

> FDA will approve an application and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.[11]

Thus, if the deficiencies in the labeling are more than "editorial or similar minor deficiencies," FDA will not approve the labeling or the application. If FDA determines that it will not approve the application in its present form for one or more of the reasons given in 21 CFR 314.125, FDA will send the applicant a "complete response" letter.[12] In the complete response letter, the Agency describes the specific deficiencies identified in an NDA or ANDA.[13]

iii. Statutory and Regulatory Standards For Five-Year NCE Exclusivity

The Hatch-Waxman Amendments provided certain incentives for NDA sponsors, including exclusivity to delay competition from applications submitted under section 505(b)(2) or 505(j) of the FD&C Act if certain conditions are met. Congress recognized that periods of exclusivity would help provide incentives for drug manufacturers to engage in the costly and resource-intensive process of researching and developing new drugs to bring to market in the United States.[14] The relevant provision states:

> If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved . . . no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the *date of the approval of the application* under subsection (b) of this section . . . .[15]

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[10] Id. See also, id. at 314.105(d) (the approval of an ANDA "becomes effective on the date of the issuance of the agency's approval letter unless the approval letter provides for a delayed effective date. An approval with a delayed effective date is tentative and does not become final until the effective date").

[11] 21 CFR 314.105(b).

[12] 21 CFR 314.110(a).

[13] 21 CFR 314.110(a)(1).

[14] See H.R. Rep. No. 98-857, Pt. I, at 15, reprinted in 1984 U.S.C.C.A.N. 2647, 2648.

[15] Section 505(j)(5)(F)(ii) of the FD&C Act (emphasis added); see also section 505(c)(3)(E)(ii) of the FD&C Act.

Thus, the statute includes clauses describing both eligibility for 5-year NCE exclusivity (eligibility clause) and the parameters of such exclusivity once it attaches (bar clause). Under the eligibility clause, a drug is eligible for 5-year NCE exclusivity if it is "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other" 505(b) application. Once a drug has met the requirements of the eligibility clause, the bar clause prevents the submission of any ANDA or 505(b)(2) application that "refers to the drug for which the [505(b)] application was submitted." This bar on submission lasts for "five years from the date of the approval of the [505(b)] application."[16] This bar (i.e., 5-year NCE exclusivity) does not block the submission, review, or approval of a 505(b)(1) application.

In 1989, FDA published a proposed rule interpreting and implementing the 5-year and 3-year exclusivity statutory provisions, along with other provisions of the Hatch-Waxman Amendments (Proposed Rule).[17] FDA finalized its regulations in 1994 without substantive changes to the exclusivity-related provisions proposed in the Proposed Rule (Final Rule).[18] The regulations, as finalized, describe 5-year NCE exclusivity as follows:

> If a drug product that contains a new chemical entity was approved . . . in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application . . .[19]

This provision uses several terms that are defined in 21 CFR 314.108. One such term is "date of approval," which is defined by FDA as:

> the date on the letter from FDA stating that the new drug application is approved, whether or not final printed labeling or other materials must yet be submitted as long as approval of such labeling or materials is not expressly required. "Date of approval" refers only to a final approval and not to a tentative approval that may become effective at a later date.[20]

The preamble to the Proposed Rule further elaborates on the definition of date of approval:

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[16] Id. A 505(b)(2) application or an ANDA may be submitted after the expiration of 4 years from the date of approval if the 505(b)(2) application or ANDA contains a certification of patent invalidity or noninfringement to a patent listed for the referenced drug. This certification is also referred to as a paragraph IV certification. Section 505(j)(2)(A)(vii)(IV) of the FD&C Act; see 21 CFR 314.108(b)(2)-(3); see also section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act.

[17] FDA, "Abbreviated New Drug Application Regulations," Proposed Rule, 54 FR 28872 (July 10, 1989).

[18] FDA, "Abbreviated New Drug Applications; Patent and Exclusivity Provisions," Final Rule, 59 FR 50338 (October 3, 1994).

[19] 21 CFR 314.108(b)(2). This regulation also permits submission of applications submitted under section 505(b)(2) or 505(j) of the FD&C Act 4 years after approval of an application for an NCE in the circumstances described in supra note 16. All references to 5-year exclusivity in this response should be understood to include this exception.

[20] 21 CFR 314.108(a).

> The "date of approval" of the application as used in these provisions means the date on the approval letter sent by FDA to the applicant. A requirement in the approval letter for submission (but not for approval) of final printed labeling or other material that might delay the actual initiation of marketing of the product is not relevant to a determination of the date of approval, so long as the product could be legally marketed.[21]

In the preamble to the Proposed Rule,[22] the Agency cites to two cases that support FDA's interpretation of "date of approval," *Mead Johnson Pharmaceutical Group v. Bowen*[23] and *Norwich Eaton Pharmaceuticals, Inc. v. Bowen.*[24] In both cases, the plaintiffs claimed that the date of approval did not start until FDA approved the drug's final labeling. The preamble to the Proposed Rule underscores that both courts agreed with FDA's position that the date an approval letter issues is the date of approval of an NDA.

iv. Drug Scheduling Under the Controlled Substances Act

Many effective and commonly prescribed drug products[25] present a potential for abuse. To enable appropriate therapeutic access to these drugs, Congress enacted the CSA, which created a system that categorizes drugs based on their accepted medical use, potential for abuse, and safety or dependence potential. Under the CSA, each category, known as a "Schedule," is associated with several requirements and restrictions. Schedule I drugs have a high potential for abuse, have no accepted medical use in treatment in the United States, and lack accepted safety for use of the drug under medical supervision; Schedule II drugs have a high potential for abuse, may lead to severe psychological or physical dependence, and have an accepted medical use in treatment in the United States or an accepted medical use with severe restrictions; Schedule III to V drugs have accepted medical uses in treatment in the United States and progressively lower abuse potentials and dependence liabilities than drugs in Schedules I and II.[26] Depending on the Schedule, controls may include manufacturing and production quotas, varying degrees of manufacturing and distribution site security requirements, dispensing and prescribing limitations, a range of record-keeping and reporting requirements, and import/export regulations.[27] Practitioners, dispensers, drug manufacturers, and distributors of controlled substances are required to register with DEA.[28]

Before a drug with a potential for abuse is scheduled under the CSA, pursuant to 21 USC 811(b), the Secretary of the Department of Health and Human Services (DHHS) is required to consider

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[21] See supra note 17, 54 FR 28898.

[22] Id.

[23] 838 F.2d 1332 (D.C. Cir. 1988).

[24] 808 F.2d 486 (6th Cir.), cert. denied, 108 S. Ct. 68 (1987).

[25] Congressional Research Services, "The Controlled Substances Act: Regulatory Requirements," December 13, 2012, available at: https://www.fas.org/sgp/crs/misc/RL34635.pdf (explaining about 10-11% of drug prescriptions written in the United States are for controlled substances).

[26] See generally, 21 USC 812.

[27] See generally, 21 USC 825, 826, 827, 828, 829; see also, 21 CFR parts 1303, 1304, 1305, 1306, 1311, 1312.

[28] 21 USC 822, 823, see also, 21 CFR part 1301.

in a scientific and medical evaluation eight factors determinative of control of a drug under the CSA. The eight factors are:[29]

1. The drug's actual or relative potential for abuse;
2. Scientific evidence of the drug's pharmacological effects, if known;
3. The state of current scientific knowledge regarding the drug or other substance;
4. Its history and current pattern of abuse;
5. The scope, duration, and significance of abuse;
6. What, if any, risk there is to the public health;
7. Its psychic or physiological dependence liability; and
8. Whether the substance is an immediate precursor of a substance already controlled.

Following consideration of the eight factors, the Secretary of DHHS must make three findings and a recommendation for scheduling a substance or drug. The three required findings relate to the substance's abuse potential, legitimate medical use, and safety or dependence potential.[30] Administrative responsibilities for evaluating a substance for control under the CSA are performed for DHHS by FDA, with concurrence by the National Institute on Drug Abuse (NIDA).[31]

As part of its NDA, if a drug has potential for abuse, a sponsor must submit a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the CSA.[32] In addition, a description must be submitted "of any studies related to overdosage . . . including information on dialysis, antidotes, or other treatments, if known."[33] Sponsors are encouraged to notify FDA early in the drug development process if they believe their drug may have abuse potential and may need to be scheduled. An assessment of abuse potential may be required if the drug affects the central nervous system, is chemically or pharmacologically similar to other drugs with known abuse potential, or produces psychoactive effects such as sedation, euphoria, and mood changes.

Procedurally, the following steps occur when a sponsor submits an NDA for a drug that FDA believes may require scheduling:

1. FDA notifies DEA when an NDA is submitted to FDA "for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system" that appears to present an abuse potential.[34]

2. The Controlled Substances Staff (CSS) at FDA evaluates the drug's abuse potential. The CSS prepares a scientific analysis, including a recommendation for scheduling,

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[29] 21 USC 811(c).

[30] 21 USC 812(b).

[31] FDA, Memorandum of Understanding with the National Institute on Drug Abuse, 50 FR 9518-20 (March 8, 1985).

[32] 21 CFR 314.50(d)(5)(vii).

[33] Id.

[34] 21 USC 811(f); see also, 21 CFR 314.104.

based on a scientific and medical evaluation of all relevant and available data (including the public health risk and the sponsor's proposal for scheduling), as required by the CSA. FDA's analysis requires review of data on abuse potential submitted by the applicant. In some cases, delay in submitting necessary data by the applicant results in delay in completion of that review.

3. FDA provides its analysis to NIDA for review and comment.

4. FDA forwards the proposed scheduling recommendation to the Assistant Secretary for Health, who makes the DHHS recommendation for scheduling and transmits the recommendation to DEA. Depending on when the necessary data are made available to FDA for review and analysis, the date of that recommendation may be near, or after, the date that the NDA for the drug is approved.

5. DEA publishes a Notice of Proposed Rulemaking in the Federal Register wherein DEA proposes scheduling, describes the proposal, and requests comments from the public. After the comment period (usually 30 or 60 days) has expired, DEA reviews any comments, objections, and requests for a hearing that they have received, and publishes a Federal Register notice, either finalizing the scheduling action with an effective date or responding to the objections and hearing requests.[35]

If DEA concludes that a drug requires scheduling, the sponsor, as well as practitioners, dispensers, and distributors, must follow specific regulations related to drug labeling, manufacturing, storage, ordering, prescribing and dispensing.[36]

v. Labeling and Marketing Requirements for Controlled Substances

When DEA has scheduled a drug as a controlled substance, that drug cannot be distributed in a commercial container unless such container bears a label with an identifying CSA symbol.[37] Further, a manufacturer of a controlled substance cannot distribute such substance unless the labeling contains the identifying symbol.[38] Similarly, FDA's regulations on labeling require labeling for controlled substances to include the CSA symbol designating the schedule in which the controlled substance is listed.[39] FDA's regulations also generally require prior approval of labeling supplements proposing to include the CSA symbol designating the schedule in which the controlled substance is listed.[40] FDA, however, has authority to waive the requirement of prior approval of that labeling supplement,[41] and it commonly does so, permitting the applicant to submit a "changes being effected" (CBE) supplement for labeling changes to add the CSA

[35] See generally, 21 USC 811(a); 21 CFR part 1308.

[36] See generally, 21 CFR parts 1300-1316.

[37] 21 USC 825(a).

[38] Id. at 825(b).

[39] 21 CFR 201.57(a)(2); see also, 21 CFR 201.57(c)(10)(i), 1302.04.

[40] 21 CFR 314.70(b)(2)(v)(C), 201.57(a)(2).

[41] 21 CFR 314.90.

symbol. An applicant can market the product with the change covered by the CBE supplement upon submission of the supplement and prior to FDA approval of that supplement.

Consistent with FDA's usual process for drugs that require scheduling, FDA's approval letters for Belviq and Fycompa contained the following statement regarding marketing:

> The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you that on [], and again on [], you agreed not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when the scheduling is finalized, you will need to make appropriate revisions to the package insert, the patient package insert and the carton and immediate-container labels through supplementation of your NDA. This would include the statements detailing the scheduling of [drug product] in the labeling, as required under 21 CFR 201.57(a)(2) and (c)(10)(i).[42]

The approval letter for Vimpat contained similar language on marketing:

> We have recommended that this product be scheduled under the Controlled Substances Act. We remind you of the following statement that appears on the Form FDA 356h, "If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision." Once a final scheduling decision is made, your label must be amended to reflect the schedule.[43]

An NDA holder's agreement not to market the drug until DEA has made a final scheduling decision is included in a certification in the Form FDA 356h, Application to Market a New or Abbreviated New Drug or Biologic for Human Use.[44] The NDA holder completes and signs this form when it submits an NDA. The form contains a certification specific to the marketing of controlled substances. As noted in the Vimpat letter, the form includes the following text:

> If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.[45]

FDA will not file an NDA unless the NDA holder has completed and signed the Form FDA 356h.[46]

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[42] See http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022529Orig1s000ltr.pdf; FDA Approval Letter for 202834, October 22, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202834Orig1s000ltr.pdf.

[43] See FDA Approval Letter for NDAs 022253 and 022254, October 28, 2008, available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/022253s000,%20022254s000ltr.pdf .

[44] Form FDA 356h is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf.

[45] Id. at 3.

[46] See 21 CFR 314.101(d)(1).

B. New Chemical Entities Required to Be Scheduled

i. Belviq

On June 27, 2012, FDA issued an approval letter to Arena Pharmaceuticals, Inc.[47] for Belviq (NDA 022529), which is approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a certain initial body mass index. Lorcaserin HCl is the active ingredient and lorcaserin is the active moiety in Belviq. Belviq is the first FDA-approved drug product that contains lorcaserin. Accordingly, upon Belviq's approval, the Agency recognized 5 years of NCE exclusivity for lorcaserin. The exclusivity period commenced on June 27, 2012, the date of approval of Belviq. According to the Orange Book, the exclusivity period will expire on June 27, 2017.

During the NDA review process, FDA determined that lorcaserin had the potential for abuse and recommended that DEA schedule the drug. FDA issued a complete response letter on October 22, 2010.[48] Some deficiencies identified in the complete response letter concerned CSS's review of lorcaserin's abuse potential.[49] Arena submitted a response to the complete response letter on December 23, 2011.[50]

In the scheduling recommendation, FDA recommended that DEA place lorcaserin into Schedule IV. According to the Petition, the Assistant Secretary of Health provided to DEA the scheduling recommendation for lorcaserin on June 25, 2012.[51] The proposed scheduling order for lorcaserin was published on December 19, 2012, and the final scheduling order was published on May 8, 2013, with an effective date for the scheduling order of June 7, 2013. DEA placed lorcaserin into Schedule IV.[52]

ii. Fycompa

On October 22, 2012, FDA issued an approval letter to Eisai for Fycompa (NDA 202834), which is approved for use as an adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Perampanel is the active moiety in Fycompa. Fycompa is the first FDA-approved drug product that contains perampanel. Accordingly, upon Fycompa's approval, the Agency recognized 5 years of NCE exclusivity for perampanel. The exclusivity period commenced on October 22, 2012, the date of approval of Fycompa. According to the Orange Book, the exclusivity period will expire on October 22, 2017.

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[47] According to the Eisai Petition, Eisai has a marketing and supply agreement with Arena. See Eisai Petition at 4.

[48] See FDA Approval Letter for NDA 022529 (June 27, 2012), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022529Orig1s000ltr.pdf (stating the date on which FDA issued the complete response letter).

[49] See FDA Administrative and Correspondence Documents for NDA 022529 at 98-102, 115-116, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022529Orig1s000Admincorres.pdf.

[50] See supra note 48 (stating the date of Arena's submission to FDA's complete response letter).

[51] Eisai Petition at 9.

[52] See 78 FR 26701-26705 (May 8, 2013).

During the NDA review process, FDA determined that perampanel had potential for abuse and recommended that DEA schedule the drug. In the scheduling recommendation, FDA recommended that DEA place perampanel into Schedule III. According to the Petition, the Assistant Secretary of Health provided DEA its analysis and scheduling recommendation for perampanel "around" January 28, 2013.[53] The proposed scheduling order for perampanel was published on October 22, 2013, and the final scheduling order was published on December 2, 2013, with an effective date for the scheduling order of January 2, 2014. DEA placed perampanel into Schedule III.[54]

iii. Vimpat

On October 28, 2008, FDA issued an approval letter to UCB for Vimpat (NDA 022253 and NDA 022254), which is approved for patients aged 17 years and older for the treatment of partial-onset seizures. Lacosamide is the active moiety in Vimpat. Vimpat is the first FDA-approved drug product that contains lacosamide. Accordingly, upon Vimpat's approval, the Agency recognized 5 years of NCE exclusivity for lacosamide. The exclusivity period commenced on October 28, 2008, the date of approval of Vimpat. According to the Orange Book, the exclusivity period expired on October 28, 2013.

During the NDA review process, FDA determined that lacosamide had potential for abuse and recommended that DEA schedule the active ingredient. FDA's CSS originally recommended that DEA place lacosamide in Schedule IV.[55] The applicant, Schwarz Biosciences, Inc. (Schwarz), disagreed with the proposed schedule and appealed this proposed scheduling recommendation. In his memorandum, the Acting Deputy Director of the Office of Drug Evaluation I stated,

> ". . . The sponsor has, in effect, appealed [the Schedule IV] recommendation, and has had a telephone conference with Dr. Doug Throckmorton, Deputy Director of CDER, and staff of [the Division of Neurology Products] and CSS to discuss this. Subsequent to this conference, the sponsor *has submitted additional data* requested by Dr. Throckmorton, who will be reviewing it. Clearly, *a decision about scheduling will not have been made by the [Prescription Drug User Fee Act (PDUFA)] date (today)*. Nonetheless, we recommend that these applications be approved today, and we have come to an agreement with the sponsor on language for labeling describing the data addressing abuse potential. It is important to point out that, by signing FDA form 356H, the sponsor has agreed to not market the product until a final decision on scheduling has been made." The Approval letter will remind the sponsor of their commitment in this matter.[56]

FDA invited Schwarz to submit data to support its scheduling recommendation. Because of this disagreement and the submission of additional data by Schwarz for FDA's review, FDA could not prepare the scheduling recommendation for the Assistant Secretary of Health so that a

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[53] Eisai Petition at 9.

[54] See 78 FR 72013-72016 (December 2, 2013).

[55] See FDA Summary Review of NDA 022253 and 022254, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022253s000_022254s000_SumR.pdf.

[56] See supra note 55 at 5 (emphasis added).

decision about scheduling could be made prior to the PDUFA goal date. Nonetheless, the NDA was ready for approval, and was approved, by the PDUFA goal date.

According to the Petition, the Assistant Secretary of Health provided to DEA its analysis and scheduling recommendation for lacosamide on December 2, 2008.[57] The proposed scheduling order for lacosamide was published on March 10, 2009, and the final scheduling order was published on May 21, 2009, with an effective date for the scheduling order of June 22, 2009. According to UCB, the "Department of Justice's letter to each House of the Congress and the Comptroller General, transmitting the final rule scheduling lacosamide, was received on June 9, 2009."[58] DEA placed lacosamide into Schedule V.[59] At least one ANDA that references Vimpat has been filed by FDA.[60]

II. PETITIONERS' ARGUMENTS

Petitioners present legal, regulatory, and policy reasons that, in their view, justify a change in the Agency's interpretation on when the 5-year NCE exclusivity period should commence for applications submitted under section 505(b) of the FD&C Act. Petitioners assert that sponsors of drugs that require scheduling are situated differently with respect to 5-year NCE exclusivity than sponsors of drugs that do not require scheduling. Because the effective date of a scheduling order typically comes after FDA approves an NDA and after the 5-year NCE exclusivity period commences, and because they have agreed not to market until scheduling is complete, Petitioners claim that they have lost some of the valuable exclusivity protection that Congress awarded to NCEs.

Petitioners contend that, for NCEs that require scheduling, FDA erroneously considers the date the approval letter issued as the date of approval for exclusivity purposes.[61] Petitioners focus on the regulatory definition of *date of approval*, which is defined as the date on a drug's approval letter, "whether or not final printed labeling or other materials must yet be submitted as long as approval of such labeling or materials is not expressly required."[62] Petitioners assert that if further labeling must be submitted for approval, then the approval letter would not trigger the exclusivity period.[63] According to Petitioners, the regulatory definition of *date of approval* is written to ensure that the effective approval date for purposes of exclusivity is tied to the date that the drug can be commercially marketed.[64] Thus, Petitioners are proposing a two approval dates approach for drugs that present abuse potential and subsequent scheduling by DEA: (1)

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[57] UCB Petition at 3.

[58] Id.

[59] See 74 FR 23789-23790 (May 21, 2009).

[60] UCB Petition at 3; see also, FDA, Paragraph IV Patent Certifications, available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM293268.pdf.

[61] Eisai Petition at 12-13. UCB adopted the position presented by Eisai in its citizen petition. See UCB Petition at 4. Therefore, FDA will be citing to Eisai's Petition, unless UCB presented an argument that Eisai had not raised.

[62] Eisai Petition at 13, citing 21 CFR 314.108(a).

[63] Eisai Petition at 13.

[64] Id.

one date of approval for the NDA, tied to the date an approval letter issues, and (2) one date of approval for the start of an exclusivity period, tied to when the drug can be commercially marketed. Petitioners further maintain that an effective approval occurs only when the drug can be marketed in interstate commerce.[65,66]

Petitioners rely[67] on the preamble to the Proposed Rule, in which the Agency states that "a requirement in the approval letter for submission (but not for approval) of final printed labeling . . . that may delay the actual initiation of marketing of the product is not relevant to the determination of the date of approval, so long as the product could be legally marketed."[68] Petitioners assert that they could not legally market their products until FDA approves labeling incorporating the final scheduling.[69] In support of their position, Petitioners focus on three regulatory requirements:[70]

(1) FDA's Form FDA 356h, on which companies with drugs subject to the CSA state a commitment to refrain from marketing the product prior to scheduling;
(2) FDA's regulations on labeling, which require labeling to incorporate the CSA symbol after a drug is scheduled; and
(3) FDA's regulations on supplements and other changes to an approved application, which require approval of a labeling change that incorporates the CSA symbol.[71]

On the basis of these requirements, Petitioners contend that they did not have an "effective" approval for purposes of NCE exclusivity until the scheduling process was complete.[72]

Petitioners also distinguish their approvals from the approvals in the two legal decisions described in the preamble to the Proposed Rule: *Norwich Eaton Pharmaceuticals, Inc. v. Bowen* and *Mead Johnson Pharmaceutical Group v. Bowen.* According to Petitioners, in *Norwich*

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[65] Id. Petitioners cite to section 505(a) of the FD&C Act, "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of [a new drug] application . . . is effective with respect to such drug." The related regulations similarly state that, "[a] new drug product . . . may not be marketed until an approval is effective." 21 CFR 314.105(a).

[66] Petitioners each propose different dates that should be considered the first day the drug product can be commercially marketed. Eisai contends that NCE exclusivity should begin either on "the day the CBE supplement is submitted with the necessary label changes" that include the CSA symbol after the scheduling order has been published or "the date the DEA scheduling order becomes effective." Eisai Petition at 15. On the other hand, it appears that UCB is claiming that NCE exclusivity should begin on the date of receipt of the Department of Justice's final rule scheduling lacosamide. UCB Petition at 3. Because we are denying the Petitions, we decline to resolve this discrepancy here.

[67] Eisai Petition at 13-14.

[68] See supra note 17, 54 FR 28898.

[69] Eisai Petition at 14.

[70] Id.

[71] As Eisai notes, approval of the labeling change is not required before marketing is permitted: "The label of a product — such as BELVIQ® or FYCOMPA™ — that undergoes CSA scheduling is routinely approved to include the CSA symbol through a changes-being-effected (CBE) supplement after a determination by the review division that a prior-approval supplement is not necessary." Eisai Petition at 15.

[72] Eisai Petition at 14.

Eaton, the drug was subject to rescheduling, and FDA said in the approval letter that the rescheduling did not affect the plaintiff's ability to market the drug in the current scheduling.[73] Petitioners state that the plaintiff in *Norwich Eaton* made a business decision not to market their drug product until the rescheduling order was final. Unlike in *Norwich Eaton*, Petitioners assert that they could not commercially market their products despite FDA's issuance of the approval letters. Further, they contend that business reasons did not drive their decision not to market, but rather FDA's regulatory framework limited their ability to commercially market their drugs that required scheduling.[74]

Further, Petitioners claim that in *Mead Johnson,* there was no requirement that FDA approve labeling before the company could market their product.[75] Unlike *Mead Johnson*, Petitioners contend that FDA expressly prohibited Petitioners from marketing their products until the CSA symbol was incorporated into the labeling, and that required approval of that labeling.[76] Petitioners also maintain that the plaintiffs in *Norwich Eaton* and *Mead Johnson* did not have to sign a Form FDA 356h that contained the certification on marketing of drugs subject to the CSA and that 21 CFR 314.108 did not exist at the time FDA approved the plaintiffs' drugs.[77]

III. AGENCY RESPONSE

Petitioners ask that FDA determine that the date of approval that starts the 5-year NCE exclusivity period for each drug is the date that the drug could be commercially marketed in interstate commerce, and not the date FDA approves the NDA for the drug. In essence, Petitioners ask FDA to decide that there are two approval dates for their drugs: (1) when FDA has completed its review of the NDA and issues an approval letter, and (2) when DEA has completed its scheduling process, with only the latter being considered for purposes of 5-year NCE exclusivity. However, the FD&C Act and FDA regulations governing drug approvals contemplate only a single date of approval, which is the date FDA issues an approval letter, unless there is a delayed effective approval, i.e., a tentative approval. Accordingly, as discussed below, the Agency declines to adopt the two approval dates approach that Petitioners propose.

The 5-year NCE exclusivity provision clearly contemplates a single date of approval for determining when the exclusivity period begins. The bar clause prevents the submission of any

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[73] Eisai Petition at 16.

[74] Eisai Petition at 16-17.

[75] Eisai Petition at 17.

[76] Commenter Hetero USA counters that the cases cited by Petitioners simply illustrate FDA's consistent position, upheld by the courts, that approval of an NDA occurs on the day of the FDA approval letter. See Hetero Comment at 4-5. It also points to another decision, interpreting a related statute also dependent on the date of FDA approval of an NDA, 35 USC 156(d), in which the court explicitly rejected the argument made by Petitioners that inability to market because of a delay in DEA scheduling meant that the date of the FDA approval letter was not the date of approval of the NDA, *Unimed, Inc. v. Quigg*, 888 F. 2d 826 (Fed.Cir. 1989). See Hetero Comment at 5. There, because the drug had to be rescheduled from Schedule I in order for marketing to be permissible under the Controlled Substances Act, the FDA approval letter noted that the drug could not be legally marketed until the rescheduling process had been completed. 888 F. 2d at 827. The court declined to accept the argument, made here by Petitioners, that *Mead Johnson* and *Norwich Eaton* were distinguishable on that ground, and found that it was bound to consider that FDA approval had occurred on the date of the approval letter.

[77] Eisai Petition at 18.

ANDA or 505(b)(2) application that "refers to the drug for which the [505(b)] application was submitted," and this bar on submission lasts for "five years from *the date of the approval* of the [505(b)] application."[78] Thus, the FD&C Act provides that exclusivity runs from the date of approval of the NDA. FDA regulations state that approval occurs on the date FDA issues an approval letter for an application,[79] unless the approval has a delayed effective date.[80] For each of Petitioners' drugs, the approval was effective on the date that FDA issued an approval letter, as there was no delayed effective date.

The statutory and regulatory provisions governing drug approvals contemplate only full approvals of NDAs, except when the standards for tentative approval apply for applications submitted under section 505(b)(2) or 505(j) of the FD&C Act.[81] Neither the statute nor FDA's regulations provide for, or envision, conditional or two-tiered approvals.

The FD&C Act specifically directs the Agency to approve a product unless one of the delineated bases in section 505(d) of the FD&C Act applies.[82] Similarly, as described above, 21 CFR 314.105(a) concerns the approval of NDAs, and states that FDA "will approve an application and send the applicant an approval letter if none of the reasons in [21 CFR] 314.125 for refusing to approve the application applies."

Petitioners' argument that their NDAs were both approved and not approved on the date FDA issued their approval letters is not supportable. Nor, upon analysis, is there support for their assertion that their NDAs were not approved at all before DEA scheduling was completed. There was never any confusion about when the NDAs in question were approved by FDA. For each of the drugs in question, the approval letter was titled, in bold and all capital letters, "**NDA APPROVAL**". Each letter stated clearly that the NDA "is approved, effective on the date of this letter." FDA regulations are clear that, with exceptions not applicable here, an "approval becomes effective on the date of issuance of the approval letter."[83] Moreover, pursuant to 21 CFR 314.107(a):

> A drug product may be introduced or delivered for introduction into interstate commerce when approval of the application or abbreviated application for the drug product becomes effective. [With exceptions not applicable here], approval of an application or abbreviated application for the drug product becomes effective on the date FDA issues an approval letter under §314.105 for the application or abbreviated application.

At the time they received the FDA approvals, Petitioners understood that FDA had approved their NDAs, and Petitioners informed their stockholders and the public that FDA had approved the NDAs.[84]

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[78] Section 505(j)(5)(F)(ii) of the FD&C Act (emphasis added); see also section 505(c)(3)(E)(ii) of the FD&C Act.

[79] 21 CFR 314.108(b)(2).

[80] See 21 CFR 314.105.

[81] Section 505(j)(5)(B)(iv)(II)(dd) of the FD&C Act; 21 CFR 314.105(a), 314.107.

[82] Section 505(c)(1)(A) of the FD&C Act.

[83] 21 CFR 314.105(a).

[84] See e.g., Eisai Announces FDA Approval of FYCOMPA™ (perampanel) for the Adjunctive Treatment of Partial-Onset Seizures in Patients with Epilepsy Age 12 and Older (Oct. 22, 2012), http://www.prnewswire.com/news-

Nevertheless, Petitioners insist that an effective approval occurs only when the drug can be legally marketed in interstate commerce.[85] This misconstrues the statute and regulations, which state that a drug cannot be marketed unless FDA has approved an NDA for that drug, but do not guarantee that the drug can be marketed when the approval is issued.[86]

As Petitioners point out, applicants for drugs subject to scheduling make a commitment, in the Form FDA 356h that is part of the NDA, not to market their products until scheduling occurs. This is one of several commitments that the applicant makes in filing the form, most of which apply to the applicant after approval of the application.[87] The NDA approval process is highly

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releases/eisai-announces-fda-approval-of-fycompa-perampanel-for-the-adjunctive-treatment-of-partial-onset-seizures-in-patients-with-epilepsy-age-12-and-older-175316181.html; Arena Pharmaceuticals and Eisai Announce FDA Approval of BELVIQ® (lorcaserin HCl) for Chronic Weight Management in Adults who are Overweight with a Comorbidity or Obese (June 27, 2012), http://invest.arenapharm.com/releasedetail.cfm?ReleaseID=687182; UCB's Vimpat® Approved By U.S. FDA As Adjunctive Therapy For Partial Onset Seizures In Adults (Oct. 29, 2008), http://www.medicalnewstoday.com/releases/127354.php.

[85] Eisai Petition at 13, citing to section 505(a) of the FD&C Act and 21 CFR 314.105(a).

[86] For example, FDA does not withhold approval of section 505(b)(1) NDAs based on patents. If a drug is claimed by a patent not held by or licensed to the applicant, when FDA approves the NDA, the FD&C Act does not prevent marketing, but marketing may violate patent law.

[87] See Form FDA 356h, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf. This is the full commitment section of the form:

> **CERTIFICATION**
>
> I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:
>
> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
>
> 2. Biological establishment standards in 21 CFR Part 600.
>
> 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
>
> 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
>
> 5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
>
> 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
>
> 7. Local, state, and Federal environmental impact laws.
>
> If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
>
> The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.
>
> **Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

dependent on the probity of NDA applicants and FDA fully expects that applicants will keep their commitments. In most cases, however, the commitments apply only after NDA approval, and failure to keep any of the commitments, if it occurred, would occur only after approval.

Drug companies like Petitioners have a responsibility to the public they serve, both the patients who use their drugs and persons who might abuse them in the absence of appropriate controls. To FDA's knowledge, no company has chosen to ignore its commitment and market its product prior to DEA scheduling when FDA has recommended that the drug be scheduled.[88] Indeed, there are obvious practical reasons why a company would choose not to market before scheduling is completed. Launching a new product without controls in place and then explaining the restrictions that had been imposed by those controls after scheduling occurred would be difficult. The company would potentially forfeit the trust of the physicians who might prescribe their products, and there could be potential product liability risks.[89]

As noted, Petitioners point to the FDA regulation that defines "date of approval" as follows:

> Date of approval means the date on the letter from FDA stating that the new drug application is approved, whether or not final printed labeling or other materials must yet be submitted *as long as approval of such labeling or materials is not expressly required.* "Date of approval" refers only to a final approval and not to a tentative approval that may become effective at a later date.[90]

Petitioners argue[91] that because they would need to submit revised labeling after scheduling in a supplement that FDA would approve, their situation falls within the highlighted exception to this regulation. But the approval letters for the drugs at issue here do not "expressly require" approval of labeling or other materials. The letters do not even impliedly require such approval, as FDA has generally permitted products of this type to be marketed after submission of a "changes being effected" supplement as soon as scheduling occurs (and before FDA approves that supplement). This is because FDA has already evaluated the abuse potential of the drug and recommended placement in a schedule; thus, it need not evaluate labeling that references the final DEA scheduling order after that order issues.[92]

As Petitioners point out, FDA will not file an NDA that does not include a signed Form FDA 356h. No company has refused to sign the form–or sought to submit a form with the certification deleted–and contested an FDA decision to refuse to file the NDA on that ground. If a company should do so, it would have the opportunity to argue that the certification is not an appropriate part of the NDA during the appeals process provided by FDA regulations. 21 CFR 314.101(f). Should that occur, FDA would consider that question in that context, but that assertion is not presented here. Petitioners signed the form without objection with respect to each drug at issue.

[88] As commentators have noted, "To date, sponsors with an approved drug with a pending scheduling decision have determined the responsible course is to hold off marketing until scheduling is complete," Mehler and Fox, FDLI Primer -- Controlled Substances: FDA and DEA Regulation of Pharmaceuticals (2012) at 31.

[89] Because no company has ever chosen that course, FDA has not had to consider what, if any, regulatory options it would have if a company did market after FDA approval and before DEA scheduling that FDA had recommended.

[90] 21 CFR 314.108(a) (emphasis added).

[91] Eisai Petition at 12-13; UCB Petition at 5.

[92] The highlighted language is an exception to the general rule, and FDA has always construed that exception narrowly. PhRMA, in a comment supporting Petitioners, has argued that this exception can only have been intended to apply to scheduling situations (despite the fact that it has never been applied to such situations). PhRMA comment at 5-6. FDA is aware of one situation, which did not involve scheduling, in which this narrow exception

Ultimately, Petitioners, by arguing that the approval letter that they received is not really an approval of their NDAs, are asserting that they should not have received an approval but instead should have received a form of "complete response letter," a communication that, under FDA's regulations, states that FDA can "not approve the application . . . in its present form" and explains what additional information must be submitted before approval can be granted.[93] But Petitioners did not seek such a response before they received their approval letters.

Finally, in response to Petitioners' contention that Congress intended a sponsor to enjoy five years of NCE exclusivity that does not begin until the sponsor is able to begin marketing, we note that Congress tied the start of the exclusivity to the date of approval, not to the date of first marketing of the product, as it did for the 180-day exclusivity provided certain ANDA applicants in section 505(j).[94]

As discussed, FDA concludes that the FD&C Act and FDA's regulations do not support Petitioners' proposed two approval dates approach.[95] FDA agrees with Petitioners that 5-year exclusivity is an important statutory incentive afforded to companies who research and develop new chemical entities. However, under the existing statutory framework, there is only a single date of approval, and an exclusivity period begins on that date.[96]

IV. CONCLUSION

FDA understands that Petitioners have lost valuable marketing time during the 5-year NCE exclusivity period. But the Agency declines to adopt the two approval dates approach that is proposed in the Petitions. The legal and regulatory framework on exclusivity and drug approvals contemplate only a single date of approval for determining when exclusivity begins for an NDA. For each NDA at issue, that date is the date that FDA completes its review and issues an approval letter.

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has been applied. In that case, the letter announcing the approval of the NDA contemplated the later submission of a trade name that FDA would have to review and approve prior to marketing, and FDA determined that the approval date was the date when the trade name was approved. The drug involved in that case was Razadyne ER (NDA 021615); see http://invest.arenapharm.com/releasedetail.cfm?ReleaseID=687182.

[93] See 21 CFR 314.110.

[94] Compare section 505(j)(5)(B)(vi)(I) of the FD&C Act ("[s]ubject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days *after the date of the first commercial marketing* of the drug (including the commercial marketing of the listed drug) by any first applicant") (emphasis added). A bill has recently been introduced in Congress that would expedite the DEA scheduling process, but that bill does not seek to change the 5-year NCE exclusivity provision. See H.R. 4299, 113th Cong. "Improving Regulatory Transparency for New Medical Therapies Act" (2014).

[95] Because the Agency is denying the Petitions, we decline to address Petitioners' arguments on the Administrative Procedure Act on adopting a new policy.

[96] FDA understands the equitable arguments made by Petitioners, and is actively considering whether it should change its approach going forward, perhaps to an approach of issuing complete response letters to drugs subject to scheduling rather than approval letters in appropriate circumstances.

For the reasons described in this response, your Petitions are denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research