DATE: September 15, 2017

TO: Adzenys ER (amphetamine) extended-release oral suspension (NDA 204325) File
Dyanavel XR (amphetamine) extended-release oral suspension (NDA 208147) File
Mydayis (mixed salts of a single-entity amphetamine product) extended-release capsule (NDA 022063)

FROM: CDER Exclusivity Board

SUBJECT: Whether the 3-year exclusivity for Dyanavel XR (NDA 208147) or Mydayis (NDA 022063) blocks the approval of Adzenys ER (NDA 204325)

This memorandum addresses whether the unexpired 3-year exclusivity the Food and Drug Administration (FDA) recognized for Dyanavel XR (amphetamine) extended-release (ER) oral suspension (Dyanavel XR) (NDA 208147) or that recognized for Mydayis (mixed salts of a single-entity amphetamine product)[1] ER capsule (NDA 022063) blocks approval of Adzenys ER (amphetamine) ER oral suspension (NDA 208147) (Adzenys ER).

Dyanavel XR was approved on October 19, 2015, for the treatment of attention deficit-hyperactivity disorder (ADHD) and received 3-year exclusivity, which is denoted in FDA's Orange Book as "new product" (NP) exclusivity. Mydayis was approved on June 20, 2017, for the treatment of ADHD in patients 13 years and older and also received 3-year exclusivity, which is denoted the Orange Book as NP exclusivity. Upon review of the administrative record related to the approval of NDAs 208147 and 022063, the Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER), in consultation with the Division of Psychiatry Products (Division), recommends that neither the exclusivity recognized for Dyanavel XR nor the exclusivity recognized for Mydayis should block approval of Adzenys ER.

The Board has determined that Dyanavel XR's exclusivity-protected condition of approval for which new clinical investigations were essential to approval is the oral ER suspension formulation[2] associated with its drug release profile. Similarly, the Board concludes that Mydayis's exclusivity-protected condition of approval is the oral ER capsule formulation[3] associated with its drug release profile. Because Adzenys ER comprises a different formulation that results in a drug release profile different from that of Dyanavel XR and Mydayis, the Board

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[1] FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) identifies the mixed amphetamine salts as follows: amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccarate, and dextroamphetamine sulfate.

[2] The term "formulation" as used in this memo includes aspects of the product's formulation that contribute to its drug release mechanism and resulting pharmacokinetic (PK) profile.

[3] Id.

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10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

recommends that the approval of Adzenys ER should not be blocked by the exclusivity for Dyanavel XR or Mydayis.

A discussion of the Board's reasoning follows.

I. FACTUAL BACKGROUND

A. History of Amphetamine Approvals

Amphetamines are a central nervous system stimulant used to treat ADHD and have a long history of use in many FDA-approved drug products. Amphetamine (its base and salts) contains two active moieties: levo-amphetamine and dextroamphetamine (*l*- and *d*-amphetamines). Amphetamines were first approved by FDA in NDA 011522 for Adderall (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate) tablets on January 19, 1960.[4] The initial amphetamine formulations, including Adderall, were immediate-release (IR) formulations and often required dosing multiple times a day.

The shift in clinical practice to day-long treatment of ADHD symptoms led to the development of modified-release (MR) amphetamine products with a biphasic release profile and once-daily dosing.[5] The Agency approved NDA 021303 for Adderall XR, held by Shire Development, LLC (Shire) on October 11, 2001, as the first MR amphetamine product. Adderall XR contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from Adderall XR compared to the conventional Adderall (IR) tablet formulation.[6] Adderall XR contains the same mixed amphetamine salts as the IR formulation, Adderall. (b) (4)

(b) (4)

Approval of Adderall XR was supported by two clinical efficacy studies (Studies 381.201 and 381.301). Study 201 was intended to assess the safety and efficacy of three doses of Adderall XR compared to placebo and IR Adderall, with all study treatments administered once daily. The study was a randomized, double-blind, 5 treatment crossover study.[9] Assessments of treatment response were obtained in laboratory classroom settings. The Swanson, Kotkin, Agler,

[4] See 35 FR 12652 (Aug. 8, 1970) for Drug Efficacy Study Implementation (DESI) findings for amphetamines.

[5] McGough JJ, Biederman J, Greenhill LL, McCracken JT, Spencer TJ, Posner K, Wigal S, Gornbein J, Tulloch S, and Swanson JM, 2003, Pharmacokinetics of SLI381 (Adderall XR) an Extended Release Formulation of Adderall. *J. Am. Acad. Child Adolesc. Psychiatry* 42(6):684-691.

[6] Woodcock Response Letter, Docket No. FDA-2005-P-0120 (Jun. 22, 2012) at 2.

[7] Id.

[8] Id.

[9] NDA 021303, Clinical Review (Oct. 6, 2001) at 6.

M-Flynn, and Pelham Rating Scale (SKAMP) was the primary efficacy measure.[10] Study 301 was intended to assess the safety and efficacy of Adderall XR in the treatment of children with ADHD. The study was a multicenter, randomized, parallel group, 4-arm, placebo controlled trial. The designated primary efficacy measure was the 10 item Conners Global Index Scale by the teacher (CGIS-T).[11]

Subsequent to Adderall XR, FDA approved three other MR amphetamine products: Dyanavel XR, Adzenys XR-ODT, and Mydayis.

1. Dyanavel XR

On December 19, 2014, Tris Pharma, Inc. (Tris Pharma) submitted NDA 208147 for Dyanavel XR (amphetamine) extended-release oral suspension, 2.5 mg amphetamine base per ml (eq. 2.5 mg base/mL),[12] for the treatment of ADHD with a once-daily dosing regimen. Tris Pharma's NDA was submitted as a 505(b)(2) application that relied upon FDA's findings of safety and effectiveness for Adderall (mixed amphetamine salts) immediate-release (IR) tablets (Teva Women's; NDA 011522). The active moieties in Dyanavel XR are *d*- and *l*-amphetamine. Dyanavel XR comprises an ion-exchange resin (polystyrene sulfonate) complexed with amphetamine to provide an extended-release profile for once daily treatment of symptoms of ADHD.[13] This product was formulated to provide convenience for patients who prefer oral dosage forms but have difficulty swallowing pills or capsules, especially pediatric patients.[14]

To support the safety and efficacy of Dyanavel XR, Tris Pharma conducted a dose-optimized, randomized, double-blind, placebo-controlled study in pediatric subjects 6-12 years of age with ADHD (Study TRI102-ADD-001).[15] Assessments for ADHD symptoms and behaviors were measured by SKAMP and Permanent Product Measure of Performance (PERMP) assessments in an abbreviated analog classroom at each clinical site.[16] The pre-specified efficacy endpoints were based on change from pre-dose baseline SKAMP score to evaluation time (4 hours after dose was the primary endpoint), and multiple evaluation times were tested (1, 2, 4, 6, 8, 10, 12, and 13 hours after dose). Two secondary endpoints of interest were measured: time of onset of clinical effect and duration of clinical effect.[17]

In addition to Study TRI102-ADD-001, the sponsor also conducted a pharmacokinetic (PK)

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[10] Id.

[11] Id. at 10.

[12] (b) (4)
(b) (4)

[13] NDA 208147, Division Director Review (Oct. 19, 2015) (Dyanavel Div. Director Review) at 2

[14] Id. See also NDA 208147, Clinical Review (Oct. 19, 2015) (Dyanavel Clinical Review) at 2

[15] Dyanavel Clinical Review at 6-8.

[16] Id.

[17] Dyanavel Div. Director Review at 2.

study in children (6 – 12 years), and a single-dose relative bioavailability and food effect trial in healthy adult subjects to support this application.[18] The Division determined that an adequate link was established between the amphetamine ER oral suspension and amphetamine IR tablets through a relative bioavailability study, and that the PK profile of amphetamine following the administration of amphetamine ER oral suspension supported once-daily dosing.[19] Total exposure ($AUC_{0-\infty}$), $AUC_{(0-t)}$ and C_{max} of both *d*- and *l*-amphetamine were equivalent between the amphetamine ER oral suspension and amphetamine IR tablets; partial(p) $AUC_{(0-4)}$ and $pAUC_{(0-5)}$ of both *d*- and *l*-amphetamine were not, however, equivalent, although $pAUC_{(5-t)}$ of *d*- and *l* amphetamine was equivalent.[20] The Agency found that the similarity of PK profiles in adults, adolescents (13 – 17 years), and children (6 – 12 years) in combination with the prior knowledge of the amphetamine IR tablet and clinical practice supported the approval and once-daily dosing recommendations in adolescents and adults.[21]

The Division determined that Study TRI102-ADD-001 supported the efficacy of Dyanavel XR in the treatment of ADHD with once-daily dosing. Dyanavel XR was approved on October 19, 2015. Dyanavel XR is the first ER oral suspension formulation of amphetamine approved. Three-year exclusivity attached to Dyanavel XR as a result of Study TRI102-ADD-001, which established efficacy of Dyanavel XR's oral suspension formulation with the product's specific drug release profile for once-daily dosing. The exclusivity, which expires on October 19, 2018, is denoted as NP exclusivity in the Orange Book.

2. Adzenys XR-ODT

On December 27, 2012, Neos Therapeutics, Inc. (Neos) submitted a 505(b)(2) NDA for amphetamine extended-release (XR) orally disintegrating tablets (ODT), tradename Adzenys XR-ODT, for the treatment of ADHD with a once-daily dosing regimen (NDA 204326).[22] The strengths for which approval was originally sought by the sponsor were (b) (4) mg, but these were changed to strengths of 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg base amphetamine. The NDA relied upon FDA's findings of safety and effectiveness for Adderall XR.

The active moieties in Adzenys XR ODT are *d*- and *l*-amphetamine. Adzenys XR-ODT contains amphetamine, in a 3:1 ratio of *d*- to *l*- amphetamine and is the first amphetamine product formulated in an ER ODT dosage form.[23] (b) (4)

(b) (4)

[18] Dyanavel Clinical Review at 5.

[19] Dyanavel Clinical Review at 4, referencing NDA 208147, Non-Clinical Review (Sep. 21, 2015) (Dyanavel Clinical Pharmacology Review at 7).

[20] Id.

[21] Dyanavel Clinical Pharmacology Review at 3.

[22] Neos resubmitted the NDA on July 27, 2015, almost two years after it received a complete response letter dated September 24, 2013.

[23] Adzenys XR-ODT Clin. Pharm. Review at 8.

(b) (4)

The Adzenys XR-ODT development program was based on a single-dose bioequivalence (BE)/food effect clinical study (Study NT0202.1005) demonstrating similarity in PK profile and exposure between Adzenys XR-ODT and Adderall XR, and assessing the effect of food on the pharmacokinetics of Adzenys XR-ODT.[25] No additional clinical safety and efficacy studies were submitted in this application. Study NT0202.1005 demonstrated that Adzenys XR-ODT provided a comparable rate and extent of drug exposure as Adderall XR.[26] The Agency determined that Adzenys XR-ODT exhibited a similar PK profile and drug absorption as Adderall XR and thus was expected to have similar efficacy and safety profiles as Adderall XR.[27] Adzenys XR-ODT was approved on January 27, 2016.

3. Mydayis

On July 21, 2006, Shire submitted a 505(b)(1) NDA 022063 for Mydayis, an ER capsule comprising the same mix of amphetamine salts as in Adderall and Adderall XR, and received an approvable letter on May 18, 2007. On December 20, 2016, Shire submitted a complete response to the approvable letter.[28] The rationale for the Mydayis formulation was to extend the benefits from the 12-hour duration of effect expected for Adderall XR to 16 hours with use of Mydayis.[29] The active moieties in Mydayis XR are *d*- and *l*-amphetamine. The Mydayis ER capsule contains three types of drug-releasing beads, which provide immediate release, (b) (4) delayed release, and delayed, extended release of the mixed amphetamine salts.[30] The clinical development program consisted of 16 clinical studies, 13 of which were included in the original NDA and 3 of which were included in the resubmission.

Approval of Mydayis was supported by two clinical efficacy studies (Studies SHP465-306 and SHP465-305). Study 306 was a phase 3, randomized, double-blind, multicenter, placebo-controlled, forced-dose titration, safety and efficacy study in adults aged 18 to 55 years with ADHD. The primary measure of efficacy was the clinician administered ADHD Rating Scale with Adult Prompts (ADHD-RS With Prompts). The study demonstrated that reduction from baseline in ADHD-RS With Prompts total score was significantly greater in the Mydayis

[24] Id.

[25] Id.

[26] The 90% confidence intervals for the log-transformed exposure parameters C_{max}, AUC_t, AUC_∞, $AUC_{5-\infty}$ were within the 80-125% range for *d*- and *l*-amphetamine. NDA 204326, Cross-Discipline Team Leader Review (Jan. 27, 2016) at 3.

[27] Id.

[28] NDA 022063, Cross-Discipline Team Leader Review (Jun. 20, 2017) (Mydayis CDTL Review) at 1.

[29] Id.

[30] NDA 022063, Clinical Review (Jun. 20, 2017) (Mydayis Clinical Review) at 8.

treatment groups (12.5 mg and 37.5 mg) compared with the placebo treatment group.[31] Study 305 was a phase 3, randomized, double-blind, multicenter, placebo-controlled, dose-optimization, safety and efficacy study in children and adolescents aged 6 to 17 year with ADHD. The primary measure of efficacy was the clinician administered ADHD Rating Scale, DSM-IV (ADHD-RS-IV). The study demonstrated that reduction from baseline in ADHD-RS-IV total score was significantly greater in the Mydayis treatment groups (12.5 mg or 25 mg) compared with the placebo treatment group.

Mydayis was approved on June 20, 2017, and is indicated for treatment of ADHD in patients 13 years and older.[32] Three-year exclusivity attached to Mydayis as a result of studies SHP465-306 and SHP465-305, which established efficacy of the Mydayis formulation, with its specific drug release profile. The exclusivity, which expires on June 20, 2020, is denoted as NP exclusivity in the Orange Book.

B. Adzenys ER

On November 15, 2016, Neos submitted a 505(b)(2) NDA for Adzenys ER, an amphetamine ER oral suspension, 1.25 mg/mL, for the treatment of ADHD with a once-daily dosing regimen, relying on the listed drug Adderall XR (NDA 021303). The active moieties in Adzenys ER are *d*- and *l*-amphetamine. Adzenys ER is a suspension of *d*- and *l*-amphetamine (b) (4) (b) (4) for oral administration. A portion of the amphetamine is IR, and a portion is (b) (4) for delayed release of amphetamine.[33] (b) (4) (b) (4) (b) (4)

Adzenys ER is intended to be an extension of the Adzenys product line. As with Adzenys XR-ODT, Neos did not conduct any clinical efficacy studies to support approval of Adzenys ER.[35] Rather, Neos relied for approval on FDA's findings of safety and effectiveness for Adderall XR.[36] Neos supported this reliance through the submission of comparative bioavailability studies. The pivotal comparative bioavailability study (Study NT021.1008) demonstrated that Adzenys ER is bioequivalent to Adderall XR.[37] As described in the Clinical Pharmacology Review for NDA 204325, Adzenys ER had a similar PK profile to Adderall XR, and therefore,

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[31] Mydayis CDTL Review at 5.

[32] The Mydayis labeling includes a limitation of use noting that pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of adverse reactions, mainly insomnia and decreased appetite. See Mydais labeling available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022063s000lbl.pdf.

[33] NDA 204325, Clinical Review (Aug. 28, 2017) (Adzenys ER Clinical Review) at 7.

[34] NDA 204325, Clinical Pharmacology Review (Aug. 28, 2017) (Adzenys ER Clin. Pharm. Review) at 2.

[35] Adzenys ER Clinical Review at 13.

[36] Id.

[37] Adzenys ER Clin. Pharm. Review at 11.

the safety and efficacy of Adzenys ER would be expected to be similar to that of Adderall XR.[38] A suspension dose of 18.8 mg is equivalent to 30 mg of Adderall XR, and the suspension can be dosed as 5, 10, 20, 25, or 30 Adderall XR-equivalent mg.[39]

II. SUMMARY OF LEGAL BACKGROUND[40]

Section 505(c)(3)(E)(iii) and (c)(3)(E)(iv) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes which applications are eligible for 3-year exclusivity, as well as which 505(b)(2) NDAs will be barred or blocked from approval by another application's 3-year exclusivity. Under the Agency's interpretation of this statutory provision, for a single-entity drug to be potentially barred or blocked by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety(ies) as the drug with 3-year exclusivity. As discussed in greater detail in Appendix A, 3-year exclusivity provides the holder of an approved NDA limited protection from new competition in the marketplace for the exclusivity-protected "conditions of approval," which FDA has interpreted to be the innovation represented by its approved drug product that is supported by new clinical investigations essential to approval. Thus, when a 505(b)(2) application for a single-entity drug seeks approval for the same drug (active moiety(ies)) to which exclusivity has attached, FDA will examine the conditions of approval supported by the new clinical investigations (other than bioavailability studies) that were essential to approval of the application with exclusivity.

If a pending 505(b)(2) application for a single-entity drug is seeking approval for the same drug for an exclusivity-protected condition of approval, the pending application will be blocked from approval for the exclusivity-protected condition of approval until the exclusivity period expires. Three-year exclusivity does not extend beyond the scope of the approval for the NDA and does not cover aspects of the drug product for which new clinical investigations were not essential to approval. Therefore, 3-year exclusivity does not block approval of a pending 505(b)(2) application containing the same drug (active moiety or moieties)that is not seeking approval for an exclusivity-protected condition of approval for the approved NDA with exclusivity.

As explained in greater detail in the appendix, the scope of 3-year exclusivity for a drug product may be affected by a previous approval for a drug product containing the same active moiety or moieties. The exclusivity protected condition of approval, and thus the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety. A drug product may, however, qualify for exclusivity for a condition(s) of approval that differs from the conditions of approval of the earlier-approved drug product. In sum, because 3-year exclusivity generally covers only a different condition(s) of approval from any previously approved product with the same active moiety or moieties, as a practical matter a later-approved product is likely to have a narrower scope of exclusivity than the product approved previously with the same active moiety or moieties.

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[38] Id.

[39] Adzenys ER Clinical Review at 7.

[40] A more detailed description and analysis of relevant statutory and regulatory provisions is provided in the appendix to this memorandum.

III. DISCUSSION

Dyanavel XR and Mydayis both have unexpired 3-year exclusivity. Dyanavel XR, Mydayis, and Adzenys ER are all "single-entity" amphetamine products with the same active moieties, *d* and *l*-amphetamine. The Board must therefore consider whether Neos is seeking approval of Adenzys ER for any of the exclusivity-protected conditions of approval for Dyanavel XR or Mydayis such that the 3-year exclusivity FDA recognized for either Dyanavel XR or Mydayis blocks approval of Adzenys ER.

As stated above, FDA interprets the scope of 3-year exclusivity for a particular product to be related to the scope of the underlying new clinical investigations that were essential to the approval of the product. Given the close relationship between plasma concentration and clinical effect of amphetamines, without evidence that the proposed product provides a rate and extent of drug exposure comparable to that of a listed drug, a demonstration of clinical efficacy throughout the day is especially important. As Dyanavel XR did not provide a rate and extent of exposure comparable to the listed drug relied upon (Adderall IR), Study TRI102-ADD-001 was essential to demonstrate the safety and efficacy of Dyanavel XR's formulation and associated drug release profile.[41,42] Accordingly, Dyanavel's formulation and associated drug release profile is the innovation protected by exclusivity. Thus, because Dyanavel XR is a different formulation with a different drug release profile than Adzenys ER, Dyanavel XR's exclusivity should not block approval of Adzenys ER.

In the case of Mydayis, the product was developed and is formulated to extend the 12-hour duration of effect for Adderall XR to 16 hours. Studies SHP465-306 and SHP465-305 were conducted to demonstrate safety and efficacy of the Mydayis formulation with its particular drug release profile (which results in an expected duration of clinical effect of 16 hours). The Mydayis formulation with its particular drug release profile is the innovation represented by Mydayis for which clinical investigations were essential. In contrast, Adzenys ER, as noted above, is formulated with a different drug release profile than Mydayis. Because Adzenys ER is a different formulation with a different drug release profile than Mydayis, the exclusivity recognized for Mydayis should not block approval of Adzenys ER.

IV. CONCLUSION

For the reasons described above, the Board recommends that neither Dyanavel XR's exclusivity nor Mydayis's exclusivity should block approval of Adzenys ER.

Reena Raman -S

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[41] See CDER Exclusivity Board Memo to NDAs 204326 and 208147 (Jan. 27, 2016) assessing whether Dyanavel XR's exclusivity blocks approval of Adzenys XR-ODT.

[42] In contrast, as described in section I.A.2, even though Adzenys XR-ODT was the first amphetamine orally disintegrating tablet to be approved, no clinical efficacy study was necessary because the product demonstrated a rate an extent of drug absorption comparable to that of Adderall XR.

APPENDIX

Legal and Regulatory Background for Exclusivity Determinations

I. Drug Approval Pathways Under the FD&C Act

Section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) new drug applications (NDAs), (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs).

A. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[43] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling, and it meets other applicable requirements.[44]

B. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[45] amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.[46] The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[47] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be

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[43] See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include: a full list of the articles used as components of the proposed drug product; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. Id.

[44] See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

[45] Public Law 98-417 (1984).

[46] Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously-approved conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

[47] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[48]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the "full reports" requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[49] Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as: its own studies; published reports of studies to which the applicant has no right of reference; the Agency's findings of safety and/or effectiveness for one or more previously approved drugs; or a combination of these and other sources to support approval.[50]

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity (NCE),[51] and, in some instances, may describe a drug product with substantial differences from a listed drug.[52] When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can *bridge*[53] its proposed product to the previously approved product by submitting, for

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[48] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

[49] Section 505(b)(2) of the FD&C Act provides for approval of an application:

> for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not 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 . . . .

See 21 CFR 314.3(b) (defining *right of reference or use*).

[50] See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA's transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

[51] See 21 CFR 314.108(a) (defining *new chemical entity*).

[52] In October 1999, the Agency issued a draft guidance for industry entitled "Applications Covered by Section 505(b)(2)" (505(b)(2) Draft Guidance) which states that "[a] 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference." 505(b)(2) Draft Guidance at 3, available at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

[53] The "bridge" in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

example, studies that measure the relative bioavailability (BA)[54] of the two products, or other appropriate scientific information.

FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process, the 505(b)(2) Draft Guidance, and previous citizen petition responses.[55] FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. FDA's interpretation of section 505(b)(2) avoids requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval, with no corresponding benefit to the public health. In addition, the conduct of duplicative studies may raise ethical concerns because it could subject human beings and animals to medically or scientifically unnecessary testing. The 505(b)(2) pathway permits sponsors and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the drug on which the 505(b)(2) application seeks to rely.[56]

II. Three-Year Exclusivity Under the FD&C Act

A. General Framework

An application for a drug containing a previously approved active moiety (including a 505(b)(2) application) is generally eligible for 3 years of exclusivity if the statutory and regulatory standards are satisfied. The statute and regulations for 3-year exclusivity describe which original NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval by that exclusivity.

For NDAs, section 505(c)(3)(E)(iii) of the FD&C Act states:

> *If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if*

[54] Bioavailability data provide an estimate of the amount of the drug absorbed, as well as provide information related to the pharmacokinetics (PK) of the drug. See, e.g., FDA's Draft Guidance for Industry: "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" (March 2014) (BA/BE NDA/IND Draft Guidance), at 3.

[55] See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

[56] 21 CFR 314.54(a) states that a 505(b)(2) application "need contain only that information needed to support the modification(s) of the listed drug."

> *such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant*, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[57]

The first clause (italicized) in section 505(c)(3)(E)(iii) of the FD&C Act, often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. FDA has interpreted the term "active ingredient" in the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean active moiety. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for single-entity drugs that are not eligible for 5-year NCE exclusivity (because they contain an active moiety "that has been approved in another application")[58] are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA's implementing regulations interpret certain aspects of the statutory language regarding 3-year exclusivity. Among other things, they define the terms *clinical investigation*,[59] *new clinical investigation*,[60] *essential to approval*,[61] and *conducted or sponsored by the applicant.*[62]

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[57] See Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4)(iv).

[58] The longest and most protective period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity. See section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act. A 5-year exclusivity period is provided 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 [section 505(b)]." For single-entity drugs, this exclusivity generally has been interpreted to prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug. Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

[59] "Clinical investigation" is defined as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects." 21 CFR 314.108(a).

[60] "New clinical investigation" is defined, in relevant part, as "an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 CFR 314.108(a).

[61] "Essential to approval" means "with regard to an investigation, that there are no other data available that could support approval of the NDA." 21 CFR 314.108(a).

[62] "Conducted or sponsored by the applicant" is defined, in relevant part, as "that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation." 21 CFR 314.108(a).

The second clause in section 505(c)(3)(E)(iii) of the FD&C Act (underlined), often referred to as the bar clause, describes which 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity. The Agency's interpretation of the bar clause and thus a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) involves two steps. One step of the scope inquiry focuses on the drug at issue. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause. The term "drug" in the eligibility clause refers to "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application," that is, the drug which includes a previously approved active moiety. Thus, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity.[63]

The second step of the scope inquiry focuses on the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant determines the "conditions of approval" for which certain subsequent applications are barred.

Although neither the statute nor the regulations defines the phrase *conditions of approval* for purposes of determining the scope of 3-year exclusivity,[64] the preamble to FDA's proposed rule governing exclusivity (1989 Proposed Rule)[65] provides the Agency's interpretation. It makes clear FDA's view that 3-year exclusivity covers the innovative change that is supported by the new clinical investigations:

> Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.[66]

FDA thus interprets the scope of exclusivity to be related to the scope of the underlying *new clinical investigations* that were essential to the approval. Exclusivity does not extend beyond

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[63] See Letter from Janet Woodcock, M.D., Director, CDER, FDA to William H. Carson, M.D., President & CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. and Ralph S. Tyler, Esq., Venable L.L.P. (Oct. 5, 2015) (Docket No. FDA-2015-P-2482), aff'd *Otsuka Pharmaceutical Co. v. Burwell*, Case No. 1:15-cv-01688-KBJ (D.D.C. July 28, 2016) (upholding FDA's conclusion that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity), aff'd *Otsuka Pharmaceutical Co. v. Price*, No. 16-5229 (D.C. Cir. Aug. 29, 2017).

[64] 21 CFR 314.108(a) and 314.108(b)(4)(iv).

[65] See generally, Abbreviated New Drug Application Regulations, 54 FR 28872 (July 10, 1989) (1989 Proposed Rule).

[66] 1989 Proposed Rule at 28896-97.

the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential. Courts have upheld FDA's view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year exclusivity.[67]

Thus, in the case of an application submitted for a single-entity drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval (i.e., the conditions of approval for which new clinical investigations were essential).

B. Effect of Previously Approved Drug Products on Scope of 3-Year Exclusivity

Generally speaking, the scope of 3-year exclusivity for a drug product may be affected by a previously approved drug product containing the same active moiety. In practice, where two single-entity drug products that have the same active moiety are sequentially approved, the result may be that the scope of exclusivity of the second drug product is limited – often narrower in scope – relative to any exclusivity recognized for the first drug product. This "narrowing" concept, and its statutory and regulatory basis, is described below.

As stated above, 3-year exclusivity provides the holder of an approved NDA limited protection from new competition in the marketplace for the exclusivity-protected "conditions of approval," which FDA has interpreted to be the ***innovation represented by its approved drug product*** that is supported by new clinical investigations essential to approval.[68] Exclusivity is recognized only for new clinical investigations that are "essential to approval," which "means, with regard to an investigation, that there are no other data available that could support approval of the NDA."[69]

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[67] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 115-24 (D.D.C. 2015); *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement'"); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) ("[T]he Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . ."). Although the latter two cases involved the parallel statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.

[68] 1989 Proposed Rule at 28896-97.

[69] 21 CFR 314.108(a). *See* 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994) ("The phrase 'essential to the approval' suggests that the clinical investigations that warrant exclusivity must be vital to the application or supplement . . . '[T]o qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective.'" (internal citations omitted)); 1989 Proposed Rule at 28900 ("In addition, there must not be an already approved drug product for which the applicant

Exclusivity does not cover aspects of the drug product for which new clinical investigations were not essential.

This link between the scope of exclusivity and the new clinical investigations essential to approval means that, in assessing the scope of 3-year exclusivity for a single-entity drug product containing the same active moiety as a previously approved single-entity drug product, the Agency looks at the innovative change(s) represented by the later-approved drug product relative to the previously approved drug product. Exclusivity for the later-approved drug product cannot cover any condition of approval for which "new clinical investigations" were not "essential." If an earlier-approved drug product was approved for a particular condition of approval, new clinical investigations would not be considered "essential" to support the same condition of approval for a later-approved drug product containing the same active moiety. Rather, the new clinical investigations would be considered essential only to support a condition of approval for the later-approved drug product that is different from the condition of approval of the earlier-approved drug product. Because 3-year exclusivity generally covers only the differences from a previously approved product, as a practical matter a later-approved product is likely to have a narrower scope of exclusivity than the product approved previously.

FDA believes that this interpretation of the statutory language is consistent with Congressional intent. The legislative history indicates that Congress intended 3-year exclusivity to protect only innovations that required the support of new clinical investigations essential to approval.[70] Under FDA's interpretation, the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety. A drug product may, however, qualify for exclusivity for an aspect that differs from the earlier-approved drug product, thus providing a continued exclusivity incentive – albeit one that is typically narrower in effect – to conduct new clinical investigations of previously approved drugs.

An example helps illustrate this interpretation in practice:

- The scope of exclusivity based on new clinical investigations that establish ***for the first time*** that an active moiety previously approved only as a single-entity, IR oral drug product can be formulated as a safe and effective extended-release oral drug product could potentially block approval of subsequent 505(b)(2) NDA for a single-entity, extended-release drug product containing that active moiety.

- Any determination of the scope of exclusivity for a subsequent 505(b)(2) NDA for an extended-release drug product containing the same active moiety would generally follow the framework described above in which the innovative change(s) represented by this product would be assessed relative to the first approved extended-release product. If, for instance, the subsequent product uses different extended-release technology for which

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could submit an ANDA or 505(b)(2) application. . . . A study will not be considered essential to approval merely because it was necessary for the applicant to conduct the study to avoid the exclusivity of the pioneer and obtain an immediate effective date of approval.").

[70] See 59 Fed. Reg. at 50358.

new clinical investigations were essential, the scope of exclusivity for this subsequent product would only cover this innovative change.[71]

[71] See Letter from R. Albrecht, FDA to M. McGuiness, Veloxis Pharmaceuticals, Inc., at 45-49 (Jan. 12, 2015).

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/s/

BRENDAN MUOIO
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