U.S. FOOD & DRUG ADMINISTRATION

DATE: April 20, 2017

TO: Xtampza ER Capsules (NDA 208090) File
Roxybond IR Tablets (NDA 209777) File

FROM: CDER Exclusivity Board

THROUGH: Sharon Hertz, MD, Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

SUBJECT: Whether the Scope of 3-Year Exclusivity for Xtampza ER (NDA 208090) Based on Study CP-OXYDET-21 Blocks Approval of RoxyBond (NDA 209777)

SUMMARY

New Drug Application (NDA) 208090 for Xtampza ER, an extended-release, abuse-deterrent (AD) oxycodone formulation for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate," was approved on April 26, 2016.[1] To support approval of NDA 208090 under the pathway described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the applicant, Collegium Pharmaceutical, Inc. (Collegium), relied upon the Agency's finding of safety and efficacy for OxyContin (oxycodone hydrochloride (HCl), controlled-release tablets) (NDA 022272), and also submitted data from its own clinical investigations, including an efficacy trial (CP-OXYDET-08)[2] and a human abuse liability (HAL) study (CP-OXYDET-21) assessing deterrence of intranasal abuse. These two studies were found to be new clinical investigations essential for approval of the Xtampza ER NDA.[3] Based on these studies, the Agency subsequently recognized that Xtampza ER was eligible for 3-year exclusivity, and denoted this exclusivity in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) with an "NP" (New Product) exclusivity code. This exclusivity expires on April 26, 2019.

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[1] The term "initial approval" will be used to refer to this date in this memorandum.
[2] Because this efficacy study (CP-OXYDET-08) demonstrated efficacy for Xtampza ER as an extended-release product for a chronic pain indication, and RoxyBond is an immediate-release product seeking approval of an acute pain indication, any exclusivity derived from this study demonstrating efficacy would not block the approval of RoxyBond. Accordingly, we will not further discuss this study in this memorandum.
[3] See Exclusivity Summary at 5. Note that the Exclusivity Summary also listed CP-OXYDET-24, a HAL study assessing deterrence of abuse by the oral route as a study upon which exclusivity could be based. That study, however, did not support an oral abuse deterrence claim in the labeling of Xtampza ER at the time of initial approval, and therefore was not essential to the initial approval of Xtampza ER. Thus, this study will not be addressed in this memorandum.

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In light of a pending application for RoxyBond immediate-release (IR) Tablets (NDA 209777) (RoxyBond), an oxycodone HCl tablet product with AD claims in the proposed labeling,[4] the Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER) is assessing the scope of 3-year exclusivity for Xtampza ER based on study CP-OXYDET-21, an intranasal HAL study. As described below, Xtampza ER's exclusivity derived from this study must be assessed in light of a previously approved drug sharing the same active moiety, OxyContin, which FDA approved with labeling describing the expected reduction of abuse via the intranasal route due to physicochemical properties. The Board, in consultation with CDER's Division of Anesthesia, Analgesia, and Addiction Products (DAAAP or Division) and other components of FDA, concludes that Xtampza ER's exclusivity based on study CP-OXYDET-21 covers the specific formulation of Xtampza ER associated with its intranasal AD properties. Because RoxyBond's formulation associated with its intranasal AD properties is different from that of Xtampza ER, it does not share any exclusivity-protected conditions of approval of Xtampza ER. The Board thus recommends that 3-year exclusivity of Xtampza ER should not block approval of RoxyBond.

A discussion of the Board's rationale follows.

I. LEGAL AND REGULATORY BACKGROUND

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the FD&C Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs). Because Xtampza ER is a 505(b)(2) application, the remaining discussion will focus primarily on the 505(b)(2) pathway.

1. 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.[5] 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,

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[4] The NDA for RoxyBond (oxycodone HCl), IR tablets (5, 15, or 30 mg oxycodone HCl) was submitted on December 29, 2013. Xtampza ER contains oxycodone base as the active ingredient, whereas OxyContin and RoxyBond contain oxycodone HCl as the active ingredient. However, Xtampza ER, OxyContin, and RoxyBond share the same active moiety—oxycodone. For the purposes of this memorandum, the term "oxycodone" refers to the active moiety.

[5] 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.

recommended, or suggested in the proposed labeling, and it meets other applicable requirements.[6]

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

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[7] 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.[8] 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.[9] 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 possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[10]

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.[11] 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.[12]

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

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

[8] 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.

[9] 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.

[10] 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).

[11] 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*).

[12] 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.

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity (NCE),[13] and, in some instances, may describe a drug product with substantial differences from a listed drug.[14] 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*[15] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability (BA)[16] 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.[17] 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.[18]

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).

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

[14] 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.

[15] 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.

[16] 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 Guidance for Industry: "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" (March 2014) (BA/BE NDA/IND Guidance), at 3.

[17] 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).

[18] 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."

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

1. 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 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.[19]

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")[20] 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

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

[20] 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.

the terms *clinical investigation,*[21] *new clinical investigation,*[22] *essential to approval,*[23] and *conducted or sponsored by the applicant.*[24]

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.

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,[25] the preamble to FDA's proposed rule governing exclusivity (1989 Proposed Rule)[26] 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

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[21] "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).

[22] "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).

[23] "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).

[24] "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).

[25] 21 CFR 314.108(a) and 314.108(b)(4)(iv).

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

> 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.[27]

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 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.[28]

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).

For supplements to approved NDAs, section 505(c)(3)(E)(iv) of the FD&C Act states:

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

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[27] 1989 Proposed Rule at 28896-97.

[28] *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.

Although the statute and regulations use different words to describe 3-year exclusivity for an original NDA and a supplement to an NDA, FDA has taken a consistent approach to both types of applications in determining eligibility for 3-year exclusivity and scope of exclusivity. The eligibility clause in section 505(c)(3)(E)(iv) (italicized) corresponds to the eligibility clause in section 505(c)(3)(E)(iii) of the FD&C Act, except, among other things, in section 505(c)(3)(E)(iv), the word "supplement" is substituted for the word "application" in section 505(c)(3)(E)(iii). As with an original NDA, a supplement may be eligible for 3-year exclusivity if it contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the supplement that were conducted or sponsored by the applicant submitting the supplement.[29]

The bar clause of section 505(c)(3)(E)(iv) (underlined) describes 3-year exclusivity as blocking approval of a 505(b)(2) application for "a change approved in the supplement." Although this language is not identical to the phrase "conditions of approval of such drug in the approved subsection (b) application" used in section 505(c)(3)(E)(iii), FDA has interpreted the language similarly and conducts the same two-step inquiry described above to determine the scope of exclusivity and which applications are barred. As explained above, one step of the inquiry focuses on the drug at issue. Under FDA's interpretation of section 505(c)(3)(E)(iv) of the FD&C Act, 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. If the 505(b)(2) application for a single-entity drug seeks approval for the same drug (active moiety) to which exclusivity has attached, then the second step of the scope inquiry applies. FDA must determine what exclusivity-protected change was approved in the supplement. To do so, FDA examines the conditions of approval supported by the new clinical investigations that were essential to approval of the supplement. If the 505(b)(2) application for a single-entity drug is for the same drug for the same exclusivity-protected change approved in the supplement, it will be blocked. However, 3-year exclusivity does not block a 505(b)(2) application for the same drug that does not seek approval for the exclusivity-protected change approved in the supplement.

2. 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.[30] 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

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[29] See 21 CFR 314.108(b)(5).

[30] This memorandum describes the analysis for single-entity drug products because Xtampza ER is a single-entity oxycodone product.

approval,"[31] which FDA has interpreted to be the ***innovation represented by its approved drug product*** that is supported by new clinical investigations essential to approval.[32] 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."[33] 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.[34] 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:

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[31] As described above in section II.B.1, FDA interprets the phrases "conditions of approval of such drug in the approved subsection (b) application" and "change approved in the supplement" to mean the same thing for purposes of determining the scope of 3-year exclusivity. For convenience, FDA uses the term "conditions of approval" throughout this memorandum.

[32] 1989 Proposed Rule at 28896-97.

[33] 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 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.").

[34] *See* 59 Fed. Reg. at 50358.

- 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 drug product can be formulated as a safe and effective extended-release 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 new clinical investigations were essential, the scope of exclusivity for this subsequent product would only cover this innovative change.[35]

C. Labeling of AD Opioids

On January 24, 2006, FDA published a final rule describing the "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," which revised the content and format requirements to make labeling easier to access, read, and use.[36] This final rule is commonly referred to as the Physician Labeling Rule (PLR). PLR format refers to labeling that meets the content and format requirements at 21 CFR §§ 201.56(d) and 201.57.

Section 9 of the labeling under PLR describes information on the drug's abuse and dependence, as appropriate.[37] Relevant here, section 9.2 of the labeling "must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used."[38]

In April 2015, the Agency issued guidance titled "*Abuse-Deterrent Opioids —Evaluation and Labeling*" (April 2015) (AD Opioids Guidance),[39] intended to assist industry in developing new formulations of opioid drugs with AD properties. Among other things, the AD Opioids Guidance explains the Agency's current thinking on including information in a drug's labeling on its AD properties based on premarket studies.

The Agency recommends that a sponsor's development program generally include three types of premarket studies to evaluate the AD properties of an opioid product:

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[35] *See* Letter from R. Albrecht, FDA to M. McGuiness, Veloxis Pharmaceuticals, Inc., at 45-49 (Jan. 12, 2015).
[36] 71 Fed. Reg. 3922.
[37] 21 CFR 201.57(c)(10).
[38] 21 CFR 201.57(c)(10)(ii).
[39] FDA, Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling, (April 2015), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf.

- Laboratory-based in vitro manipulation and extraction studies (Category 1), "to evaluate the ease with which the potentially [AD] properties of a formulation can be defeated or compromised;"[40]

- PK studies (Category 2), "to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration;"[41]

- Clinical abuse potential studies (also referred to as HAL studies) (Category 3), for assessing the impact of potentially AD properties.[42]

FDA advises sponsors to propose labeling that sets forth the results of Category 1, 2, and 3 studies (and any postmarket studies (Category 4), if available) and appropriately characterize the AD properties of the product.[43] Information on AD properties should be described in Section 9.2 of the proposed labeling. Labeling regarding abuse deterrence should describe the product's specific AD properties and the specific routes of abuse that the product has been developed to deter.[44] Specific recommendations on how to describe the results of the premarket studies are found in Section VI of the AD Opioids Guidance.

The AD Opioids Guidance also lists the seven categories of current AD formulations, including Physical/Chemical Barriers, described below:

> Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.[45]

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[40] Id. at 6.
[41] Id. at 8.
[42] Id. at 9.
[43] Id. at 22.
[44] Id.
[45] AD Opioids Guidance at 3.

II. FACTUAL AND PROCEDURAL BACKGROUND

To assess the scope of 3-year exclusivity for Xtampza ER based on study CP-OXYDET-21 in this memorandum, we must analyze the innovative changes represented by Xtampza ER for which a new clinical investigation was essential relative to relevant previously approved single-entity products containing oxycodone. For the purpose of this scope of exclusivity analysis, that relevant previously approved drug product is OxyContin, the first AD, single-entity drug product containing oxycodone.

A. OxyContin

OxyContin when first approved on December 12, 1995 (NDA 020553), was not formulated with properties to deter abuse. The labeling stated that the product should only be taken orally, and warned that taking crushed, chewed, or broken tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.

A reformulated version of this non-AD OxyContin was developed by Purdue Pharma, L.P. (Purdue) with controlled-release features that would be less easily compromised by tampering than the original non-AD OxyContin, and thereby potentially result in a reduction in abuse. Specifically, the formulation changes were intended to create a tablet that was more difficult to crush or dissolve, and more resistant to the extraction of oxycodone by chemical means. The relative abuse deterrence of this new formulation was enabled by formulating oxycodone HCl in a solid matrix of polyethylene oxide and magnesium stearate resistant to crushing and chemical extraction.[46] No new clinical efficacy studies were performed – or required – to support the original approval of this reformulated OxyContin because comparative PK studies showed that the reformulated and original non-AD versions of OxyContin had comparable bioavailability (BA).[47]

The NDA for this reformulated version of OxyContin (NDA 022272) was approved on April 5, 2010, for the same indication as the original version of OxyContin, namely "the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time." However, although the Division concluded that Purdue had provided adequate data to demonstrate that their reformulated OxyContin product would potentially be more tamper-resistant based on changes to the controlled-release formulation, less likely to result in overdose when tampered with and ingested, and less likely to be insufflatable or syringeable/injectable, the Agency under its then existing policy regarding AD opioids recommended that Purdue be required to perform certain post-marketing studies to assess the impact of the new formulation in the community before any labeling with AD claims could be approved.[48] The labeling as approved on April 5, 2010, did not provide any specific information regarding the AD properties of OxyContin.

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[46] Summary Review, NDA 022272, September 30, 2008, at 4.

[47] The NDA also consisted of CMC data, non-clinical pharmacology studies and studies that assessed the attributes of the reformulation in terms of the effects of chemical and physical manipulation intended to defeat the modified-release characteristics of the product.

[48] Summary Review, NDA 022272, April 5, 2010, at 6.

On September 14, 2012, Purdue submitted supplement 14 (S-14) to NDA 022272 requesting FDA approval of labeling describing the AD properties of the reformulated OxyContin. S-14 included data from *in vitro* manipulation and extraction, PK, clinical abuse potential (drug liking), and epidemiologic studies relevant to the potentially AD properties of OxyContin.[49] The HAL study supporting the approval of S-14, OTR 1018, was a pivotal, single-center, randomized, double-blind, positive- and placebo controlled, 5-treatment crossover study in non-dependent, recreational opioid users to evaluate the abuse potential, PK, and safety of intranasally administered finely and coarsely crushed OxyContin versus the original 1995 formulation of OxyContin, and oxycodone active pharmaceutical ingredient.[50]

The data from all these studies were evaluated together, and the totality of the evidence was assessed to determine whether, and the degree to which, the reformulated OxyContin could be expected to deter abuse relative to the original version of OxyContin.[51] S-14 was approved on April 16, 2013, with labeling describing the risks specific to the abuse of OxyContin, the results of the abuse deterrence studies (both in vitro manipulation/extraction and clinical), and the summary conclusions reached from such studies about the AD properties of the drug in Section 9.2 (Abuse & Deterrence) of the labeling. Specifically, the labeling states that "[t]he data from the clinical study [the HAL], along with support from the *in vitro* data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route."[52]

OxyContin was found to be eligible for 3-year exclusivity based on the results of the HAL study, OTR 1018. Regarding the scope of exclusivity, the Board in a memorandum dated March 3, 2015 ("OxyContin exclusivity memo"), determined that this intranasal HAL study only supported the addition of information obtained from that study to the labeling recognizing that OxyContin's physicochemical properties are expected to reduce abuse via the intranasal route.[53] The Board thus recommended that the scope of exclusivity related to S-14 be limited to the addition of information to the OxyContin labeling regarding the reduction of abuse via the intranasal route. Subsequently, the Agency recorded this exclusivity in the Orange Book, denoting it with the exclusivity code "M-153" described in the Orange Book as "Addition of Information Regarding the Intranasal Abuse Potential of OxyContin." This exclusivity expired on April 16, 2016.

In light of the evolution of the Agency's approach to assessing 3-year exclusivity for certain AD opioids put forth in a memorandum addressing the scope of 3-year exclusivity for MorphaBond (morphine sulfate) extended-release tablets (NDA 206544) dated January 9, 2017 ("MorphaBond exclusivity memo") and an addendum to the MorphaBond exclusivity memo dated April 19, 2017,[54] the Board in an addendum to the OxyContin exclusivity memo dated April 19, 2017, reassessed the scope of OxyContin's 3-year exclusivity related to S-14[55]. Applying an approach

[49] Office Director Memo, NDA 022272, April 16, 2013, at 3.
[50] Office Director Memo, NDA 022272, April 16, 2013, at 5.
[51] Office Director Memo, NDA 022272, April 16, 2013, at 11.
[52] OxyContin approved labeling, Section 9.2 (Abuse & Deterrence).
[53] OxyContin Exclusivity Memo, March 3, 2015.
[54] MorphaBond Exclusivity Memo, Jan. 9, 2017, and addendum, Apr. 19, 2017.
[55] Addendum to OxyContin Exclusivity Memo, Apr. 19, 2017.

to the scope of 3-year exclusivity for AD opioids articulated in the MorphaBond exclusivity memo in which the scope is defined by two primary characteristics: (1) the abuse route (intranasal); and (2) the type of abuse deterrence employed (physicochemical properties), the Board recommended that the scope of OxyContin's exclusivity be limited to the condition of approval supported by the intranasal HAL study, i.e., "labeling describing the expected reduction of abuse of a single-entity oxycodone by the intranasal route of administration due to physicochemical properties."[56]

This approach was found to be applicable to OxyContin, because like MorphaBond, OxyContin is the first FDA-approved, single-entity version of its opioid active moiety with a claim in the labeling related to deterring abuse via the intranasal route. Moreover, like MorphaBond, deterrence of abuse by the intranasal route is a result of the drug product's physicochemical properties.

B. Xtampza ER

Xtampza ER consists of a capsule filled with microspheres made up of a wax-based solid solution of oxycodone base in a hydrophobic matrix.[57] The microspheres (b) (4) the inactive ingredients (myristic acid, yellow beeswax, carnauba wax, and stearoyl polyoxyl-32 glycerides), (b) (4) inactive ingredients (magnesium stearate and colloidal silicon dioxide) and are then encapsulated to produce capsules that contain oxycodone base in strengths of 9 mg (equivalent to 10 mg oxycodone HCl), 13.5 mg (equivalent to 15 mg oxycodone HCl), 18 mg (equivalent to 20 mg oxycodone HCl), 27 mg (equivalent to 30 mg oxycodone HCl), and 36 mg (equivalent to 40 mg oxycodone HCl) capsules.[59]

The microspheres (b) (4) (b) (4)

[56] The Board concluded that the extended-release aspect of OxyContin was not a consideration in design of the intranasal HAL study, OTR 1018, and thus was not relevant to determining the scope of exclusivity. Therefore, it is not part of the exclusivity-protected condition of approval supported by OTR 1018. In general, HAL studies that assess deterrence of abuse through the *intranasal* route of administration do not take into account whether the proposed AD opioid product is an immediate-release or extended-release product. In other words, the design of the intranasal HAL studies does not depend on whether the proposed AD opioid is an immediate-release or extended-release product. Study OTR 1018, an intranasal HAL study, did not evaluate the abuse potential of OxyContin specifically with respect to its extended-release characteristics and therefore the extended-release aspect of OxyContin is not part of the scope of its 3-year exclusivity. Rather, the scope of OxyContin's exclusivity encompasses single-entity oxycodone products, regardless of drug release profile, that share the described conditions of approval.

[57] Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 4.

[58] Clinical Review, NDA 208090, July 29, 2015, at 15.

[59] Id. See also Xtampza ER labeling.

[60] Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 4.

(b) (4)

Collegium submitted NDA 208090 for Xtampza ER on December 12, 2014, for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate," ("chronic pain indication"). As noted above, to support approval, NDA 208090 relied on FDA's finding of safety and effectiveness for OxyContin (oxycodone hydrochloride (HCl) extended-release tablets, NDA 022272, also approved for the chronic pain indication), specifically, the safety and effectiveness of oxycodone, and the description of the pharmacology and toxicology of oxycodone in the OxyContin labeling,[63] an efficacy trial (CP-OXYDET-08), several PK studies, and two HAL studies in non-dependent, recreational users - CP-OXYDET-21, a HAL study assessing deterrence of intranasal abuse, and CP-OXYDET-24, a HAL study assessing deterrence of oral abuse.[64] Collegium also conducted a series of in vitro physical manipulation and chemical extraction studies to assess the possible AD effects of Xtampza ER.[65]

The efficacy trial, CP-OXYDET-08, was conducted to evaluate the analgesic efficacy of Xtampza ER compared to placebo because Xtampza ER is not bioequivalent to OxyContin, however, the study also attempted to evaluate a possible food effect observed earlier in development.[66] Unlike OxyContin, which contains oxycodone HCl salt, Xtampza ER contains an oxycodone base. Both OxyContin and Xtampza ER are extended-release formulations designed to be dosed twice-daily. Study CP-OXYDET-08 also included an analysis of adverse events suggestive of potential drug abuse.[67] Analysis of the pain scores reported during the trial generally supported a finding of efficacy for Xtampza ER for the chronic pain indication.[68]

Both in vitro and HAL studies were conducted to evaluate the abuse-deterrent properties of Xtampza ER. The in vitro studies focused on the ability to manipulate Xtampza ER to defeat the extended-release properties because a higher C_{max} with a more rapid rise to C_{max} are associated

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[61] Id. at 6.
[62] Quality Assessment Review, NDA 208090, Sep. 8, 2015, at 61.
[63] Pharmacology & Toxicology Review, NDA 208090, Sept. 22, 2015, at 11.
[64] Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 25; CSS Review, NDA 208090, Sept. 9, 2015, at 24.
Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 20; CSS Review, NDA 208090, Sept. 9, 2015, at 9.
[66] Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 14; Clinical Review, NDA 208090, July 29, 2015, at 25. The exposure to oxycodone from Xtampza ER was found to be less than from OxyContin in the fasted state, but closer in the fed state. In the efficacy study, the sponsor was advised to include a patient diary documenting the timing of food with respect to dosing in order to determine whether any efficacy or safety concerns arose that could be attributed to the food effect.
[67] CSS Review, NDA 208090, Sept. 9, 2015, at 46.
[68] Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 17.

with better subjective effects for the abuser.[69] To evaluate whether Xtampza ER was susceptible to particle size reduction, eleven tools/methods were tested on Xtampza ER, OxyContin tablets, and Roxicodone (oxycodone HCl) tablets.[70] While nine of these tools resulted in a less than 10% reduction in Xtampza ER's particle size, with grinding by a mortar and pestle for two minutes being the most effective, eight of these tools resulted in a change in the OxyContin tablets, ranging from deformation to small particles.[71] Attempts to syringe and inject Xtampza were less successful than with OxyContin (and Roxicodone) with substantially more oxycodone recovered from the latter.[72]

The pharmacokinetic effects of manipulation were examined as part of the evaluation of the AD effects of Xtampza ER for the intranasal route of administration in both naltrexone-blocked normal volunteers and unblocked opioid-experienced, non-dependent subjects. The studies showed that there was a much higher C_{max} from IR oxycodone powder administered intranasally, than from either oral or intranasal Xtampza ER. The clinical pharmacology review for Xtampza ER concluded that crushing and snorting the contents of the Xtampza ER capsule did not produce the relatively high plasma concentrations over a short duration that abusers seek in order to rapidly achieve a euphoric effect when manipulating and administering dosage forms via the nasal route.[73]

Of the two HAL studies, only the intranasal HAL study, CP-OXYDET-21, supported AD claims that were included in Xtampza ER's labeling. CP-OXYDET-21, was a randomized, double-blind, double-dummy, positive- and placebo-controlled, single-dose, 4-treatment, 4-period crossover study in subjects experienced with intranasal opioid abuse. The primary objective of the study was to evaluate the deterrent effects of Xtampza ER for abuse by the intranasal route of administration against the active comparator oxycodone IR tablets.[74] Crushing the oxycodone comparator resulted in a fine powder, whereas Xtampza ER when crushed resulted in larger particles by comparison.[75] Study CP-OXYDET-21 showed that intranasal administration of IR oxycodone HCl produced a maximum oxycodone plasma concentration that was significantly greater than that produced following intranasal administration of Xtampza ER.[76] Based on the measures of Drug Liking VAS (primary), High VAS (secondary) and Take Drug Again VAS (secondary) results, Study CP-OXYDET-21 showed evidence of a possible deterrent effect for abuse by the intranasal route of administration. The responses for Drug Liking and Drug High after administration of Xtampza ER intranasally were considerably lower compared to IR oxycodone for four hours following dosing.

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[69] Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 20.
[70] These included a rotating food chopper, blade-based pill cutter, cheese grater, mortar and pestle, hammer, metal garlic press, pill crusher (with teeth), pepper mill, herb mill, and coffee grinder.
[71] Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 21.
[72] Id.
[73] Clinical Pharmacology Review, NDA 208090, Sep. 8, 2015, generally.
[74] Id. at 27-28.
[75] CSS Review, NDA 208090, Sept. 9, 2015, at 37.
[76] Id. at 40.

Upon review of the application, the Agency determined that Xtampza ER has properties that resist attempts to manipulate the formulation by dissolution and small volume extraction for injection by syringe and is likely to deter abuse by the intravenous route of administration.

The Agency also concluded that Xtampza ER resists attempts to defeat the extended-release profile by physical crushing followed by oral or intranasal administration and by chewing the contents of the capsule. These findings, together with the reduction in Drug Liking and the rating to Take Drug Again following insufflation, relative to an active control, supported the Agency's conclusion that Xtampza ER is likely to deter abuse by the intranasal route of administration.[77]

Xtampza ER was approved on April 26, 2016. The Orange Book currently states that Xtampza ER has "NP" (new product) exclusivity. Xtampza ER's exclusivity will expire on April 26, 2019, 3 years after the date of the original approval.

C. RoxyBond

Inspirion Delivery Technologies, LLC (Inspirion) submitted NDA 209777 under section 505(b)(2) of the FD&C Act for RoxyBond (oxycodone HCl), IR tablets (5, 15, or 30 mg oxycodone HCl) with purported AD properties, for the "[m]anagement of moderate to severe pain where the use of an opioid analgesic is appropriate."[78] As an IR formulation, RoxyBond is intended to be administered every 4 to 6 hours.[79] This NDA has a PDUFA goal date of April 21, 2017.[80]

To achieve abuse deterrence, Inspirion claims that RoxyBond incorporates Inspirion's proprietary AD technology that makes tablets difficult to manipulate and resist extraction in widely used solvents.[81] This technology imparts physical and chemical barriers intended to make the product difficult to manipulate and abuse.[82] To achieve these objectives, a combination of excipients is used.[83] The RoxyBond tablet comprises a [redacted].[84] The excipients used in the [redacted] of the RoxyBond tablets (hypromellose and xanthan gum) [redacted].[85] The excipient used in the tablet's [redacted].[86]

To support approval of NDA 209777, Inspirion is relying on FDA's previous finding of safety and effectiveness for Roxicodone, an IR oxycodone tablet available in strengths of 15 and 30 mg

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[77] Division Director Summary Review, NDA 208090, Nov. 6, 2015, at 30.
[78] Combined Cross-Discipline Team Leader (CDTL) Review and Clinical Review, NDA 209777, Apr. 14, 2017, at 1.
[79] Clinical Pharmacology Review, NDA 209777, Mar. 22, 2017, at 1.
[80] Combined CDTL Review and Clinical Review, NDA 209777, Apr. 14, 2017, at 1.
[81] CSS Statistical Review, NDA 209777, Feb. 22, 2017, at 6.
[82] Combined CDTL Review and Clinical Review, NDA 209777, Apr. 14, 2017, at 2.
[83] CSS General Review, NDA 209777, Mar. 29, 2017, at 6.
[84] Id., at 5.
[85] Id., at 5-6.
[86] Id., at 7.

(NDA 021011), as well as published literature.[87] Inspirion conducted a clinical comparative BA study to bridge to FDA's finding of safety and efficacy for Roxicodone and a PK dose proportionality study to support marketing of the 5- and 15-mg tablet strengths.[88] No clinical efficacy study in the target pain population was conducted.[89]

To support AD claims in labeling in accordance with the AD Opioids Guidance, Inspirion conducted extensive Category 1 in vitro laboratory manipulation and extraction studies, and a combination Category 2 PK study/Category 3 HAL study.[90] The results of these studies support a claim that RoxyBond tablets will have a lower potential for abuse by intravenous injection and intranasal administration compared to crushed Roxicodone.[91]

III. DISCUSSION

At issue here is whether 3-year exclusivity for Xtampza ER based on study CP-OXYDET-21 blocks approval of the NDA for RoxyBond. An application for a drug containing a previously approved active moiety is eligible for 3-year exclusivity if the approval of the application is supported by at least one (1) new (2) clinical investigation (other than a bioavailability study) (3) that is conducted or sponsored by the applicant and is (4) essential to the approval of the application.[92] Specifically, as noted above, the intranasal HAL study, CP-OXYDET-21, was a "new clinical investigation" (other than a bioavailability study) that was "essential to the approval of the application" and "conducted or sponsored" by Collegium within the meaning of the FD&C Act and implementing regulations.

As noted in section I.B., although the FD&C Act and implementing regulations do not define "conditions of approval," the Agency interprets the scope of 3-year exclusivity to cover the "innovative change" for which the underlying new clinical investigations were essential to the approval. Accordingly, to determine the scope of exclusivity of Xtampza ER based on study CP-OXYDET-21, the Agency must determine the innovative change(s) for which a new clinical investigation was essential to the approval of the Xtampza ER application, and for which 3-year exclusivity should be recognized. In particular, as noted in section I. B, these innovative change(s) must be assessed relative to previously approved drug products containing the same active moiety.

As stated above, Xtampza ER was not the first single-entity oxycodone product approved with intranasal abuse-deterrent claims due to physicochemical properties. OxyContin was the first such product which on April 16, 2013, obtained 3-year exclusivity for the addition of certain intranasal abuse-deterrent information and claims to its labeling due to its physicochemical properties. Therefore, any analysis of the innovative change(s) represented by Xtampza ER must

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[87] Combined CDTL Review and Clinical Review, NDA 209777, Apr. 14, 2017, at 1, 4; Pharmacology/Toxicology Review, NDA 209777, Mar. 31, 2017, at 25.
[88] Combined CDTL Review and Clinical Review, NDA 209777, Apr. 14, 2007 at 1; Clinical Pharmacology Review, NDA 209777, Mar. 22, 2017, at 6, 16.
[89] Combined CDTL Review and Clinical Review, NDA 209777, Apr. 14, 2007 at 1.
[90] CSS General Review, NDA 209777, Mar. 29, 2017, at 1.
[91] Id., at 2.
[92] The approval of an NDA or supplement to an NDA includes approval of labeling submitted in the NDA or supplement. 21 CFR 314.50.

be made relative to OxyContin, which in turn must include a determination of the innovative changes represented by OxyContin over any previously approved single-entity oxycodone products, in particular those innovative changes supported by new clinical investigations essential to the approval of supplement S-14 to the OxyContin NDA. As noted above in section II.A, upon reanalysis the Agency has found that the innovative change represented by OxyContin over previously approved oxycodone products is that it is the first single-entity oxycodone product with "labeling describing the expected reduction of abuse of a single-entity oxycodone by the intranasal route of administration due to physicochemical properties."[93]

To determine the scope of 3-year exclusivity for Xtampza ER related to study CP-OXYDET-21, the Board follows the framework described in section I.B, in which the innovative change(s) represented by Xtampza ER for which a new clinical investigation was essential for its approval is assessed relative to OxyContin.

The approval of supplement S-14 for OxyContin established for the first time that a single-entity oxycodone product could be formulated with physicochemical properties expected to reduce intranasal abuse, and the resulting scope of exclusivity reflects this innovation. Xtampza ER, like OxyContin, is also a single-entity oxycodone product with physicochemical properties expected to reduce intranasal abuse. The HAL study supporting approval of Xtampza ER with an intranasal AD claim, CP-OXYDET-21, was not essential to show that a single-entity oxycodone product could be formulated with physicochemical properties expected to reduce intranasal abuse. Approval of OxyContin S-14 had already established that. Rather, the study was essential to support that Xtampza ER's particular formulation contributes to its intranasal AD properties. Specifically, Study CP-OXYDET-21 demonstrated that, as a result of Xtampza ER's specific formulation, intranasal administration of crushed Xtampza ER resulted in a substantially lower response to Drug Liking, High, and Take Drug Again measures, compared to IR oxycodone. The Board thus recommends that the scope of Xtampza ER's 3-year exclusivity based on study CP-OXYDET-21 be limited to "labeling describing the expected reduction of abuse of Xtampza ER by the intranasal route of administration due to physicochemical properties."

As explained above in section II.C, RoxyBond uses a different formulation from Xtampza ER to achieve its intranasal AD properties. Therefore, Xtampza ER's exclusivity should not block the approval of RoxyBond.

IV. CONCLUSION

For the reasons described above, the Board recommends that because the scope of Xtampza ER's 3-year exclusivity based on study CP-OXYDET-21 is related to the formulation of Xtampza ER associated with its intranasal AD properties, this scope of exclusivity be limited to "labeling describing the expected reduction of abuse of Xtampza ER by the intranasal route of administration due to physicochemical properties." Xtampza ER's exclusivity expires 3 years after the approval of the application, on April 26, 2019.

[93] Addendum to OxyContin Exclusivity Memo, Apr. 19, 2017.

The Board recommends that 3-year exclusivity of Xtampza ER based on study CP-OXYDET-21 should not block approval of RoxyBond because RoxyBond's formulation associated with its intranasal AD properties is different from that of Xtampza ER.

DAAAP concurs with this recommendation.

Sanjay Sitlani -S

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TAIYE AYOOLA
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